University of Alberta

Systemic Adjuvant Therapy in Relation to Breast Cancer Survival of Women with Breast Cancer in the Northern Alberta Population

by

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ABSTRACT

While incidence rates of breast cancer have risen during recent decades in western countries, mortality rates have declined slightly since 1985. In Alberta, incidence and mortality rates for breast cancer have paralleled those for the rest of Canada.

Although the effectiveness of adjuvant systemic treatment have been established in clinical trials since the beginning of the 1970's, there is little population-based data on outcomes associated with the introduction of adjuvant treatment into routine practice.

This study investigated whether survival in Alberta women with breast cancer is associated with the use adjuvant systemic therapy after adjusting for other prognostic factors using data from the Northern Alberta Breast Cancer and Alberta Cancer Registries.

Results demonstrated that adjuvant therapy was not associated with improved survival rates in Alberta women with breast cancer.

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CHAPTER 1

INTRODUCTION

The incidence of breast cancer is highest among all cancers affecting women in North America and in some Western European countries such as the United Kingdom and Switzerland. The United States has the highest incidence rate in the world. Canada ranks the second. The incidence of breast cancer has increased worldwide, especially in past 20 years. In the United States there has been a steady increase in the rate of breast cancer since 1950, with a sharp rise in the 1980s. The same trend has been shown in other countries such as the United Kingdom, Canada, and Sweden. The incidence rates of breast cancer have also increased in developing countries. Although incidence rates are higher for older women, breast cancer threatens women in their reproductive years with significant impacts on their working and family roles (Sondik, 1994).

Breast cancer is one of the most serious problems in the health of Canadian women. The lifetime probability of a female developing breast cancer is approximately 11 percent (National Cancer Institute of Canada, 1997). In other words, about one woman in nine can expect to develop breast cancer during her lifetime. Canadian incidence rates have risen slowly and steadily since 1969, rising most rapidly among women aged 50 and over (Gaudette, Silberberger and Gao, 1996). Breast cancer is a major cause of death in Canadian women and approximately 4.1 percent of women in Canada die from breast cancer (Statistics Canada, 1996). For women of all ages, breast cancer ranked as the fourth leading cause of death (5% of all deaths) next to ischaemic heart disease (21%),

stroke (9%) and lung cancer (5.4%) (Statistics Canada, 1996). Breast cancer was the commonest cause of death in women 45-55 years of age.

While breast cancer incidence among women has risen steadily over the past decade, the mortality rate for breast cancer has declined slightly in Canada since 1985 and particularly since 1990 (Statistics Canada, 1998). Therefore, while incidence rates are climbing mortality rates are decreasing. Similar trends have occurred in other countries. In North America and European countries except for Belgium, Hungary, Poland and Spain, the mortality rates of breast cancer generally increased in the early decades of the 20th. century. However, more recently mortality rates have begun to decline in most countries (Beral and Hermon, 1996).

In Alberta, incidence and mortality rates for breast cancer have paralleled those in other parts of Canada. Breast cancer caused 20 percent of cancer deaths among Alberta women in 1992 (Alberta Cancer Board, 1996). In 1993, breast cancer represented 30 percent of all cancers diagnosed in women. The estimated age-standardized Canadian incidence rates of breast cancer placed Alberta second highest among all the provinces in Canada (Statistics Canada, 1998).

The reasons responsible for the decline in mortality are not clear: birth cohort effects, the result of improved treatment and early detection through screening are among the variables (Tarone and Chu, 1996 & 1997). Birth cohort effects were suggestive of a decline in breast cancer mortality among women born after 1920 and were evident in many countries, particularly Canada, the Netherlands, the United Kingdom and United States (Hermon and Beral, 1996). However, this is only one factor, others must also be considered. If the fall in mortality of breast cancer is due to the improved treatment, one

would expect to see a corresponding fall in stage-specific mortality. However, if the drop in mortality rates is caused by the change of staging at diagnosis, one would expect to see little change in stage specific survival and a shift towards to earlier stages at diagnosis of breast cancer (Stockton, Davies, Day, et al, 1997). A retrospective study conducted in the UK investigated the recent fall in breast cancer mortality rates in England and Wales. However, the study results do not give clear answers to either of these hypotheses. There is some evidence to support a decline in mortality due to improved treatment. (Hermon and Beral, 1996). However, little research has been done to investigate this.

The treatment regimen is closely related to the stage of breast cancer. Staging of breast cancer serves as a guide for treatment, indicates prognosis and enables a comparison of different treatment methods (Holleb, Fink, Murphy, et al, 1991). The TNM (T: primary tumor; N: lymph node; M: distant metastasis.) system is a well-accepted standard of staging classification (stage I – stage IV) of breast cancer worldwide. Since the beginning of the 1970's, the treatment of breast cancer has been changing continuously. The primary treatment of breast cancer is still surgery. Surgical procedures include lumpectomy, partial, total or radical mastectomy. Surgical procedures that involve removing some of the breast tissue are usually combined with irradiation and dissection or sampling of the axillary lymph nodes (Swenson, Decher, et al, 1998). Patients at early stages with negative axillary nodes and treated with breast-conserving surgery (BCS) plus radiotherapy have demonstrated survival rates of 92 percent at 5 years and 83 percent at 10 years post surgery (Ariagada, Le, Rochard, et al, 1996). Studies have shown that patients who received BCS plus radiotherapy have equivalent survival rates to those who received total mastectomies with other factors being equal

(Ariagada, Le, Rochrd, et al, 1996). Some studies report higher survival rates in BCS plus radiotherapy when compared BCS alone (Jacobson, Dander, Cowan, et al, 1995).

Adjuvant treatment is defined as therapy administered to patients with no demonstrable residual tumor after the initial treatment. Chemotherapy, hormonal therapy and radiotherapy are used most commonly in adjuvant treatment (Holler, Fink, Murphy, et al, 1991).

The beneficial effects of postoperative irradiation have been shown in many studies. One study showed that the recurrence rate for patients treated with radiotherapy after surgery was three times lower than the rate with surgery alone (Early Breast Cancer Trialists' Collaborative Group, 1995). Also, several trials showed the overall survival rates and disease-free survival rates in patients treated with radiotherapy after surgery were better than that of patients with surgery alone (Fisher, Anderson, Redmond, et al, 1995).

Since the middle of 1970's, therapy regimens for breast cancer patients have changed rapidly with the introduction of chemotherapy and hormonal therapy. Following the Bonadonna's report, adjuvant chemotherapy was introduced to premenopausal women with positive axillary lymph nodes (Bonadonna, Brusamolino, Valagussa, et al, 1976). Adjuvant hormonal therapy (Tamoxifen) was used for postmenopausal women with positive nodes from the early 1980's onward (EBCTC Group, 1992).

The introduction of tamoxifen as anti-estrogen agent into clinical practice led to its subsequent use in combination with chemotherapy (Harness, Oberman, et al, 1988). Tamoxifen was evaluated for use in metastatic breast cancer from 1974 to 1977 and approved for general use in 1980. In a Scottish trial with women with node-positive

breast cancer, there was a statistically significant difference in disease-free survival in favour of women using tamoxifen at 5 years (Stewart, 1992).

However, while the effectiveness of adjuvant therapies has been established in clinical trials, there is little population-based data on outcomes associated with its introduction as routine practice. One of the early Canadian population-based studies of adjuvant systemic therapy and survival after breast cancer was carried out in British Columbia, Canada. Data were obtained from the provincial cancer registry on all cases of breast cancer in women during the calendar years 1974, 1980, and 1984. Results showed an improving trend in survival rates. For women less than 50 years of age, overall survival improved from 64.8 to 74.6 percent. For women between 50 and 89 years of age, overall survival improved from 53.9 to 58.3 percent (Olivotto, Dajadik, et al, 1994). Also, in the studies conducted by the Early Breast Cancer Trialists Group, the advantages of different systemic therapies have been demonstrated.

While breast cancer treatment is changing, breast cancer screening has also expanded since the early 1970s and the influence of early detection of breast cancer on survival has been discussed in many studies (Barchielli, Paci, Balzi, et al, 1994). The International Workshop on Screening for Breast Cancer demonstrated that regular mammographic screening for women aged 50 to 69 could reduce breast cancer mortality by about a third. However, survival rates for women aged 40 to 49 consistently demonstrated no benefit from screening in the first 5 to 7 years of the study. But in a recent study, women younger than 50 years were shown to have similar survival rates to women who were over 50 years of age (Thurfjell and Lindgren, 1994).

Besides treatment, there are some other important prognostic factors related to breast cancer survival. The stage (stage I, II, III or IV) of cancer when diagnosis is made is one of the most important determinants of survival. Women with an early stage of breast cancer (stage I or II) have better survival rates than those with advanced breast cancer (stage IV) (Mclaughlin and Sloan, 1995). Tumor size and histological grade are pathological parameters for breast cancer survival. Patients with large tumors and/or higher-grade tumors have relatively high mortality rates (Simon and Severson, 1997). Hormone receptor status and menopausal status are two biological parameters for breast cancer prognosis (Mark and Bland, 1996). The observed differences in survival have not been consistently explained by the biological differences of patients with breast cancer (Meng, Maskariner, Wikkens, 1997). Therefore, further research is needed to determine what factors are related to breast cancer survival and whether improved treatment, early detection through screening, or other reasons are responsible for the decline in mortality rates.

Study of the trends in the rates of breast cancer incidence, mortality and survival over time can provide valuable insights into the status of breast cancer in a given geographic location such as in Alberta. Many researchers have shown an interest in whether the decline in mortality rates and the possible improvement of survival rates are related to the changes in treatment. Correspondingly, much research has been focused on the survival and treatment of breast cancer patients. Currently, the association between survival and systemic treatment in breast cancer has not been sufficiently demonstrated, especially, in population-based studies (Stoll, Hihberd, Paterson, et al, 1986). In Alberta, some research has been focused on breast cancer in the past decades. Some studies

assessed survival in relation to treatment, for instance, 'Five-year Survival of Women with Breast Cancer in Northern Alberta' (Burns, Freund, Lees, et al, 1979). However, the sample size of this study was too small for significant assessment of the treatments used in primary breast cancer in Albertan women.

The Northern Alberta Breast Cancer Registry is a population-based database collected over the period of eighteen years (from 1971 to 1989). This database enables one to perform population-based investigations of women with breast cancer rather than studying highly selected groups of patients such as those enrolled in clinical trials. Since Alberta women have a high incidence of breast cancer and relatively long survival rates, further story is warranted. Studying trends in breast cancer survival rates can provide useful information for Alberta health care researchers and planners. Also, it provides an important measure of breast cancer burden in the Alberta population and on the health care system. The information can be used as a reference to plan patient services and health care facilities to meet the increasing demand.

CHAPTER 2

LITERATURE REVIEW

A large amount of breast cancer research has been carried out worldwide over the past decades, especially in Western countries. In early years, most of the published papers were based on clinical trials of breast cancer. In recent years, more literature related to population-based studies of breast cancer has been published. Many studies are focused on the decrease of mortality and improvement of survival in breast cancer.

A literature search was conducted through MEDLINE database for studies of breast cancer in women between 1968 and 1998. The search strategy was focused on breast cancer mortality, breast cancer survival, incidence of breast cancer, treatment, surgery, chemotherapy, irradiation, tamoxifen, adjuvant therapy/treatment, mammography, breast cancer screening, prognostic factor, breast cancer prognosis, histological grade. All pertinent articles were reviewed and hand searching was used for selected papers.

Tarone and Chu and their colleagues (1992) examined the impact of epidemiological effects on the divergence cross-sectional trends in breast cancer mortality with age. They examined breast cancer mortality rates from 1969 to 1988 by birth cohort for white women in the United States using a nonparametric, permutational method to analyze 2-year, age-specific mortality rates for women aged 30 to 89 years. Unequivocal interpretation of trends in birth cohort effects estimated by using standard statistical modeling of demographic data was not possible because of technical difficulties in separating linear trends in birth cohort effects from linear trends in calendar

period effects, but these authors identified the trend in rates with successive birth cohorts. The results showed the longitudinal effects have a significant impact on cross-sectional trends in breast cancer mortality. The divergence in trends with age was shown to be consistent with an increase in breast cancer risk with successive birth cohorts from 1900 to 1916 and between 1916-1926 and with a decrease in breast cancer risk with successive birth cohorts beginning around 1926. These authors stressed that longitudinal effects must be taken into account in monitoring and evaluating the effects of early detection, treatment, and intervention programs using national rates.

Tarone, Chu and Gaudette (1997) discussed the birth cohort and calendar period trends in breast cancer mortality in the United States and Canada based on the information of women born between 1924 and 1938. The purpose of this study was to compare and identify possible racial, regional, and temporal differences in breast cancer mortality rates from 1969 through 1992 for white and black women in four regions of the United States and for women throughout Canada. Differences and trends in the rates were evaluated in view of breast cancer risk factors and relevant medical interventions. Age-period-cohort models were fitted to the data, and changes in birth cohort and calendar period trends were examined. The results showed birth cohort trends for all women were similar until 1940, with a moderation of mortality risk beginning around 1924. The authors found that the slope of the mortality calendar period trend increased in the 1980s compared with the 1970s for study participants. In the last calendar period, 1991 to 1992, a trend of decreasing mortality rates was found for white women in the United States and for women in Canada, the authors found that widespread environmental exposures are unlikely to explain the higher relative rates observed for U.S. white women in the

Northeast, since the rates for black women in this region were not higher than in other regions. The increase in calendar period trend slope in the 1980s likely reflects the coincident rise in breast cancer diagnosis via mammography. The recent decline in mortality rates in the calendar period for white women in the United States and for women in Canada may be the result of earlier detection. Increased use of adjuvant therapy, particularly tamoxifen therapy was likely contributed to these decreases, although some benefit from early detection cannot be ruled out. In a third paper Chu and Tarone (1996) focused on the determinants of trends in breast cancer mortality rates, as well as incidence and survival rates by extent of disease at diagnosis, for white women in the United States and considered whether these trends were consistent with the widespread use of beneficial medical interventions. They used the mortality data from the National Center for Health Statistics and incidence and survival data by extent of disease from the National Cancer Institute, all stratified by patient age, using statistical regression techniques to determine changes in the slope of trends over time. Linear regression analyses of log-transformed rates were used to estimate the direction and magnitude of trends in breast cancer survival and mortality. Piecewise regression analyses were used to test for sudden change in slope in the linear trend in rates. Three-year relative survival rates were calculated for survival analysis and stratified by age. The results showed that the age-adjusted breast cancer mortality rate for white women in the U.S. dropped 6.8% between 1989 and 1993. A significant decrease in the slope of the mortality trend of about 2% per year was observed in every decade of age from 40 to 79 years of age. Trends in incidence rates were also similar among these age groups. Incidence rates increased rapidly between 1982 and 1987 and stabilized or increased more slowly

thereafter. Three-year relative survival rates increased steadily and significantly from 1980 to 1989 in all age groups, with no evidence of an increase in slope in the late 1980s. The authors believed that the decrease in the diagnosis of regional disease in the late 1980s in women over the age of 40 years likely reflects the increased use of mammography earlier in the 1980s. The increase in survival rates, particularly for regional disease, likely reflects improvements in systemic adjuvant therapy. Statistical modeling indicated that the recent drop in breast cancer mortality is too rapid to be explained only by the increased use of mammography. These explanations are consistent with the results of randomized clinical trials in the late 1970s and early 1980s, confirmed the benefit of adjuvant therapy.

Besides the studies conducted in the United States, the Health Statistics Division of Statistics Canada has used the data from the Canadian Cancer Registry and the National Cancer Incidence Reporting System to identify the trends in breast cancer incidence and mortality rates in Canada and possible variations between the provinces (Gaudette, Silberberger, et al., 1996). Because of delays in compiling and processing cancer related health data, estimates for recent years have been produced by modeling incidence and mortality data by province for breast cancer. Changes in the annual age-standardized breast cancer incidence and morality rates were examined by calculating the average annual percent change over time period. Observed survival was calculated using a Kaplan-Meier survival curve. Data provided by the Northern Alberta Breast Cancer Registry and Saskatchewan Cancer Registry were pooled. Data from the two registries were comparable based on visual comparison and results from Wilcoxon univariate chi-square tests. The study results showed that breast cancer was the leading form of cancer,

accounting for about 30% of all newly reported cancers. Incidence rates increase rapidly from age 30 to age 70, level off, and dropped after age 84. For women aged 40 to 49, breast cancer is the leading cancer and associated for one-third of all cancers diagnosed in this age group. Although the number of newly diagnosed cases in women aged 40 to 49 increased by 65% between 1982 and 1992, overall incidence rates are stable. The increased number of breast cancers diagnosed in this age group is thus entirely explained by the movement of baby-boomers into the over-40 age group, a trend also observed in the United States. The well-established risk factors associated with the moderate to high relative risk for breast cancer include age, country of birth, family history of breast cancer, and biopsy-confirmed benign proliferative breast disease. The risk factors associated with minor relative risks include a number of factors related to hormonal status and lifestyle factors including socioeconomic status, obesity and religion. The results also showed that mortality rates remained relatively stable at around 30 to 32 per 100,000 women between 1969 and 1990. The rate declined from 31 to 29 per 100,000 between 1990 and 1993: the lowest mortality rates since 1950. Breast cancer mortality rates declined by about 1-2% per year among women aged 30 to 59 years, however rates dropped by almost 15% between 1990 and 1993. The rates are relatively high in British Columbia, Manitoba, Saskatchewan and Nova Scotia, and low in Quebec and Newfoundland. Breast cancer survival rates are more favorable than those of most other forms of women's cancer in Canada. Data from Alberta and Saskatchewan cancer registries showed that almost 70% of women diagnosed with breast cancer can expect to live at least five more years, and about 50% can expect to live at least 10 years post diagnosis. Survival rates vary considerably by age. Women aged between 45 and 54

years have the best survival rates. Survival is also highly dependent on the stage at which the cancer was first diagnosed.

Research and analysis of time trends, age cohorts and age period models of breast cancer mortality have been conducted in many western countries. International trends in breast cancer mortality have been studied using the data provided by the World Health Organization's Division of Epidemiological Surveillance and Health Situation and Trend Assessment (Hermon and Beral, 1996). Data were provided for each year during the period 1952 to 1992 in 5-year age groups. Twenty countries were selected on the basis that data were available for at least the period 1960 to 1990. In the statistical analyses two models were derived for each country: an age-birth cohort model and an age period of death model. Log-linear Poisson models were completed using the statistical package EGRET. The main finding from this analysis was that, although breast cancer mortality rates had been increasing in most Western countries since 1950, recently mortality rates seem to have leveled off or begun to decline in many counties. The cohort effects are strongest in Canada, The Netherlands, and Sweden where cohort mortality ratios have declined for women born after 1920. The results extend and support the conclusions of others, based on data from earlier years, that breast cancer mortality rates may be declining in many Western countries. Several factors might influence a decline in breast cancer mortality rates: change in death certification coding practices, change in incidence rates due to changes in risk factors, and changes in survival due to improvements in treatment and/or earlier diagnosis. Changes in cohort mortality rates may be in part due to changes in childbearing patterns for different birth cohorts of women. The authors

discussed how the improvement in survival can also affect mortality trends. Increased survival can be achieved by early detection of tumors and effective treatment.

Stockton and Davie et al (1997) investigated the recent drop in mortality of women with breast cancer in England and Wales, and to determine the relative contributions of improvements in treatment and earlier detection of tumors. This retrospective study was based on all women diagnosed between 1982 and 1989 who were listed in the East Anglia Cancer Registry. The 3-year relative survival rates by time period, age group, and stage were measured. The relative hazard ratios for each time period and age group derived from Cox's proportional hazards models (Parmar and Machin, 1995) adjusted for single year of age and stage. The results showed that survival improved in the later time period, although there was little stage specific improvement. The proportion of earlier stage tumors increased especially in the 50 to 64 year age group, and adjustment for stage accounted for over half of the improvement in survival in women aged less than 65 years. The authors considered that the fall in mortality was more likely explained by the improvement in treatment, presenting at an earlier stage, and the increased use of tamoxifen. However, reasons for this increase in incidence of early stage tumors from 1986 onwards are unclear. The authors thought that screening do not account for it because that process did not start until 1989. However, they proposed that the increase could be due to the general increase in awareness of breast cancer and subsequent reduction in tumor size at diagnosis followed by a decline in mortality rates.

A new method for monitoring cancer patient survival was employed to assess progress in the 5-year survival of breast cancer patients in Saarland, Germany, between 1980 to 1984 and 1990 to 1994 (Brenner, Stegmaier and Ziergler, 1998). Cumulative

survival rates were calculated by calendar periods of observation rather than by cohorts with patients defined by common calendar periods of diagnosis. This analysis was based the population-based data from Saarland cancer registry. Changes in 5-year relative survival over time were tested for statistical significance using the chi-square test for linear trend between periods. The results showed that absolute survival rates gradually improved from 63.6% in calendar period 1980-84 to 68.6% in calendar period 1990-94 in all age groups combined. A similar improvement in relative survival estimates demonstrated that the improvement in survival was not due to reduced mortality from other causes. The improvement in survival was most pronounced for the age group 50-59 between calendar periods 1980-84 and 1985-89. Throughout the periods of investigation, absolute 5-year survival was lowest in age group 70-79, and relative 5-year survival was lowest in age group 50-59, despite major improvement in both age groups between calendar periods. There was only a minor improvement in prognosis among patients below age 50. They authors suggested that the possible reasons for this improvement could be due to earlier diagnosis and advancements in therapy.

A similar study had been done in Sweden, where Adami and Malker (1986) used data from The National Swedish Cancer Registry, which covered all women with a newly diagnosed breast cancer between 1960 and 1978. The purpose of the study was to investigate if the improved trend in survival could be solely explained by an increasing detection of tumors with benign biologic features or by lead-time bias among more recently diagnosed cases. The observed, expected and relative rates were calculated. The results showed that a temporal trend in improved survival was apparent in all age groups, but it was of low magnitude among women younger than 45 years of age. The authors

indicated that there was no reason to believe that the observed upward survival trend for breast cancer resulted from biases in the reporting of diagnosed cancer. Nor was it likely that the trend was the result of errors in mortality statistics. They also indicated that improved treatment was not a reasonable alternative. On the other hand, the temporal changes in the stage distribution at diagnosis were significant in this study. Also, the authors suggested that the impact of adjuvant systemic treatment on temporal trends seemed improbable as there was negligible use of the drug in Sweden during these years. However, they suggested that possible reasons for the improved trend in survival could be the changes in diagnostic criteria used by pathologists, earlier diagnosis due to mammography screening, and a changing natural history of disease. The results obtained did not support the initial hypothesis that the improved trend in survival was solely explained by an increasing detection of early diagnosed tumors. One 5-year survival study of women with breast cancer in northern Alberta was based on the data from the Northern Alberta breast Cancer Registry in 1971 and 1972 (Burns, Freund, Lees, et al., 1979). The 5-year survival rates were calculated and reported as actuarial survival, a process which adjusts for those lost to follow-up, and as relative survival. Results showed that the relative 5-year survival rate was 73%, which is higher than most rates reported from other centers. Women aged from 40 to 59 years had a higher survival rate (79%) than those under 40 years (65%) or over 60 years (66%) of age. Women between age of 35 to 39 years had particularly poor survival rates (59%). The authors found that lymph node involvement and stage were two significant prognostic factors in breast cancer survival. Post-menopausal status women had higher survival rates than those who were peri-menopausal and pre-menopausal. The authors suggested the increase in incidence

and decrease in breast cancer mortality indicated an improvement in the survival trends. But, this trend could also be related to local conditions, such as changes in age distribution, migration, epidemiological characteristics and patterns of treatment.

Many of these researchers suggested that one possible explanation for the improved trends in breast cancer survival were related to the impact of adjuvant systemic therapy on breast cancer alone. Some earlier clinical trial results on adjuvant treatment of breast cancer were reported by Bonadonna and his colleagues in a clinical trial. The purpose of this study was to evaluate the prolonged cyclic combination chemotherapy with CMF (Cyclophosphamide, Methotrexate and Fluorouracil) as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary nodes (Bonadonna, . Brusamolino, et al., 1976). The standard life-test method was used to calculate the treatment-failure time distribution. The chi-square test was calculated to determine the level of significance in proportions of treatment failures. The results of the study showed that treatment failure occurred in 24% of 179 control patients and 5% of 207 patients given combination chemotherapy, the advantage appearing statistically significant in all subgroups of patients. Results also showed that patients with positive nodes at the time of mastectomy had a statistically significant reduction in recurrence rate during the first 27 months after radical mastectomy when treated with cyclic prolonged combination chemotherapy. Bonadonna and Brusamolino (1976) stressed that these results should be considered with caution, since at that time, the effect of this therapy on survival and possible long-term side effects remained unknown.

A worldwide study of systemic treatment of early breast cancer had been conducted by the Early Breast Cancer Trialists' Collaborative Group, which gathered

information on mortality and recurrence for each woman in any randomized trial that began before 1985 of any aspect of systemic adjuvant therapy for early breast cancer. The data were available for 75,000 women. The data sets reviewed included 30,000 women in tamoxifen trials, 11,000 in polychemotherapy trials, 15,000 in other chemotherapy comparisons, and the rest in other trials. Trials were to be included only if they began randomizing patients before Jan 1, 1985, and all patients were to be included with follow-up to the date they were last known to be alive. The analyses involved all the deaths or recurrences that had been reported. The analyses both of survival and of recurrence-free survival involved the "log-rank" observed minus expected (O-E) numbers, which was used in statistical significance tests, tests of overall effect of different trials, and estimating the ratio of the annual odds of death in the treatment group to that in the controls. Also, the odds reductions of death or of recurrence were calculated. The results showed a highly significant reduction in the annual rates both of death and of recurrence were produced by tamoxifen and by polychemotherapy. The avoidance of recurrence for tamoxifen and polychemotherapy was chiefly during first 4 years, but the avoidance of mortality is highly significant both during and after the first 4 years (Early Breast Cancer Trialists' Collaborative Groups, 1992). The cumulative difference in survival made by these treatments was larger at 10 years than at 5 years. Tamoxifen demonstrated efficacy for patients aged 70 and older, but the effect of polychemotherapy was not evaluated with this group. The therapy regimen of chemotherapy plus tamoxifen was better than chemotherapy alone both for recurrence and for mortality, and better than tamoxifen alone for recurrence in women aged 50 to aged 69 years. The 30% to 40% proportional risk reductions can be produced by combination chemo-endocrine therapy in middle age

are similar for node-positive and for node-negative patients, but the absolute improvement in 10-year survival is about twice as great for the former as for the latter. The Early Breast Cancer Trialists' Collaborative Group performed a meta-analysis of 36 trials conducted before 1985 to detect the effects of surgery plus adjuvant radiotherapy (Early Breast Cancer Trialists' Collaborative Groups, 1995). For the most part, the studies compared radiotherapy plus surgery with the same type of surgery, or more-extensive surgery with less-extensive surgery plus radiotherapy. The results showed that surgery plus radiotherapy resulted in a rate of local recurrence three times lower than the rate with surgery alone, but there was no significant difference in 10-year survival.

In Alberta, studies conducted in the early 1980s assessed the effects of systemic treatment on survival in metastatic breast cancer. One study showed a trend towards improved survival from onset of first distant metastasis after 1975, which is attributed to the combined chemotherapy (Paterson, Lees, et al., 1982). The results suggested that chemotherapy might improve the short-term survival among patients, but no major impact on long-term survival was evident. Another study by these authors also assessed the influence of systemic therapy on survival in metastatic breast cancer. However, there was little evidence to support the widespread assumption that the magnitude of clinical response to the first systemic therapy a woman receives confers any survival advantage in breast cancer (Paterson, Lees, et al., 1985). On the other hand, if disease progression occurs with the first systemic therapy, survival from diagnosis of first distant metastasis is significantly shorter regardless of response to subsequent therapies. These studies focused on the systemic treatment for women with metastatic breast cancer not on the systemic adjuvant therapy for women without metastasis at the time of diagnosis.

Therefore, there is a need to study systemic adjuvant treatment in breast cancer research in Alberta.

Results of studies where the effects of surgery plus irradiation with surgery alone were compared after long-term follow-up are of interest. The study conducted by the National Cancer Institute was based on a randomized single-institute trial between 1979 and 1987 where compare the results of treatment based on lumpectomy plus axillary dissection and irradiation were compared with treatment based on mastectomy plus axillary dissection after a median potential follow-up of 10.1 years for women with stage I or stage II breast cancer (Jacobson, Danforth, et al., 1995). The results showed the 10-year overall survival rate was 75 percent for patients who underwent mastectomies and 77 percent for patients who underwent lumpectomy plus radiation. Disease-free survival at 10 years was 69 percent for women who underwent mastectomies and 72 percent for those who underwent lumpectomy plus radiation. The 10-year local regional recurrence rate was 10 percent after mastectomy, but only 5 percent after lumpectomy plus radiation. Therefore, the study demonstrated that breast conservation with lumpectomy and radiation offered the equivalent results at 10 years to that of mastectomy.

Similar results were found in a study of the National Surgery Adjuvant Breast Cancer and Bowel Project. Fisher and Anderson (1995) reanalyzed the results of a clinical trial after an average of 12 years of follow-up. The trial was performed with patients with either negative or positive axillary nodes and tumors less than 5cm in diameter. The patients were randomly assigned to three treatment groups: total mastectomy, lumpectomy plus irradiation, or lumpectomy alone. No significant differences were found in overall and disease-free survival between the three treatment

groups. However, the cumulative recurrence rate was 35% in the group treated with lumpectomy alone and 10% in the group treated with lumpectomy plus irradiation. These findings confirm that lumpectomy followed by irradiation is the appropriate treatment for women with either negative or positive nodes. Another randomized clinical trial conducted in France also showed that there was no significant difference in overall survival, distant metastasis, contralateral incidence, new primary malignancy, and local regional recurrence rates between a group treated with tumorectomy plus irradiation and a group treated with modified radical mastectomy (Arriagada, Lê, et al., 1996). The long-term results supported the efficacy of conservative treatment with tumorectomy plus systemic irradiation as a safe procedure for the management of early breast cancers. Using multivariate analysis these authors found that age, tumor size, histologic grading, and number of axillary nodes were important histologic and clinical factors for breast cancer prognosis in overall and disease-free survival.

The positive effects of adjuvant systemic therapy have also been demonstrated in other studies. Henderson's (1994) overview of randomized clinical trials indicated that the use of adjuvant chemotherapy with younger women or pre-menopausal women reduced the annual odds of death by about 25%. The use of adjuvant tamoxifen with older or post-menopausal women, especially those with estrogen receptor positive tumors, had a similar effect. The use of adjuvant tamoxifen resulted in a greater survival benefit for women with many positive nodes than for those with negative nodes. The absolute survival for patients with positive nodes was between 8% and 10%. The difference in median survival between treated and untreated patients is approximately 2 years, which might be due the use of adjuvant treatment. Moreover, the absolute effects

of adjuvant chemotherapy for patients with positive nodes were substantially higher than those with negative nodes. The same relationship was seen in the adjuvant tamoxifen studies. Patients at a lower risk of recurrence because of strongly positive estrogen receptors are more likely to benefit from adjuvant tamoxifen and other forms of endocrine treatment. It has not been established that combinations of chemotherapy and tamoxifen result in a better survival than for chemotherapy alone for younger women. Nor has it been established that tamoxifen alone benefits older women.

Although many studies have demonstrated the effects of adjuvant systemic therapy on patients with breast cancer, the results derived from most of these studies were based on randomized clinical trials. There were a few Canadian population-based studies. One population-based study conducted by British Columbia Cancer Agency includes all women with breast cancer diagnosed in British Columbia between 1974 and 1984. The method the authors used was to select three cohorts of women with primary breast cancer diagnosed in 1974, 1980, and 1984. These three calendar years separately represented the year of three different treatment recommendations: 1974, when no adjuvant chemotherapy was recommended; 1980, when adjuvant chemotherapy was recommended only for pre-menopausal women with positive nodes; and 1984, when adjuvant chemotherapy was extended to include pre-menopausal women with negative nodes and tamoxifen was recommended for post-menopausal women with positive nodes and positive estrogen receptors. The authors calculated overall survival and disease-specific survival as well as Kaplan-Meier estimates of survival. The log-rank statistic was used to test the difference between each pair of cohorts. The results showed disease-specific survival at 7 years was 65.2% in 1974 and 76.3% in 1984 for women less than 50 years

of age (Olivotto, Dajadik, et al. 1994). Overall survival rates were 53.9% in 1974 and 58.3% in 1984. There was a significant improvement both in disease-free survival and overall survival. It was concluded that the survival among British Columbia women with breast cancer improved significantly during the study period when adjuvant systemic therapy became widely available.

Many studies of breast cancer have focused on determining the correlation between adjuvant systemic therapy and the trends of decreased mortality rates of breast cancer as well as the improved trends in breast cancer survival. At the same time, there were many published articles where it was suggested that breast cancer screening was possibly responsible for the improvement in survival of breast cancer. The National Cancer Institute held an International Workshop on Screening for Breast Cancer to conduct a critical assessment of clinical trial data on breast cancer screening. Eight randomized controlled trials of breast cancer screening (with mammography and/or clinical breast examination) had been conducted. For women aged 40 to 49, none of four trials demonstrated a statistically significant rates benefit in mortality after 10 to 12 years follow-up (Fletcher, Black, 1993). A combined analysis of Swedish studies showed a statistically non-significant 13% decrease in mortality at 12 years. Only one trial showed a 25% decrease in mortality reduction after 10 to 18 years follow-up. For women aged 50-69 years, all studies showed mortality reductions about 30% at 10 to 12 years. Two of the results were statistically significant. The authors concluded that for women aged 40 to 49 years the benefit of breast cancer screening was uncertain, but women aged 50 to 69 years, screening reduced mortality by about one third.

Kopans (1994) reviewed the methodology of clinical trials evaluating the effect of breast cancer screening on mortality and found that five of the eight randomized controlled trials had demonstrated mortality reductions for women aged 40 to 49 years. However, these studies lacked of necessary statistical power as the numbers of women in these age groups were insufficient. The available data suggested that woman aged 40 to 49 years could benefit from screening, just as woman 50 to 59 years of age. In a study involving the Breast Cancer Detection Demonstration Project, a nation-wide breast cancer screening program conducted between 1973 and 1980 with women diagnosed in this period and followed through 1988 and 1989. Byrne and Smart (1994) indicated that 34.6% of cases detected by mammography alone had the highest overall breast cancer survival rates of 90.9% while 32.2% of cases detectable by both physical examination and mammography had the lowest breast cancer survival of 79.0%. They concluded that the breast cancer survival advantage for having a small tumor, no positive lymph nodes, or breast cancer detected by mammography alone was lower for women aged 40 to 49 years than women aged 50 to 59 years or older at diagnosis and these differences in survival advantage may help to account for the differences in mortality by age in the randomized clinical trials.

On the other hand, some population-based studies of breast cancer screening provided more reliable evidence for the relationship between breast cancer screening and breast cancer survival. One population-based study was conducted by Tuscany Cancer Registry in the province of Florence, Italy, between 1985 and 1986. Researchers calculated the observed survival (Kaplan-Meier method) and relative survival rates of 1263 patients with invasive breast cancer. The Cox model was used to evaluate the

effects of the possible prognostic factors and the observed survival rates compared with that in Switzerland and that in the U.S. Researchers found that the 5-year relative survival was lower in Florence than that in the other two countries (Barchielli, Paci, et al., 1994). Five-year prognosis was worst in residents of municipalities who had not been involved in the screening program. Researchers concluded that screening might have a positive effect in survival of patients with breast cancer. Another population-based mammographic screening program on breast cancer conducted in Sweden showed that the cumulative survival rates were 92% for women younger than 50 years of age and 87% for women older than 50 years of age, and the cumulative survival rate for all women with breast cancer was 88% at 7 years after diagnosis (70% of cases was detected at screening) (Thurfjell and Lindgern, 1996). Therefore, the similar survival rates for breast cancer in women younger and older than 50 years suggested that mammography screening could be effective in women aged 40 to 49 years.

Some breast cancer researchers think that the increase of incidence and improvement of survival could be possibly due to the changes in prognostic factors of breast cancer. A population-based study conducted in Scotland, the Scottish Breast Cancer Focus Group had investigated factors influencing the survival of women with early breast cancer in Scotland. Researchers used a multivariate analysis and found that some clinical factors such as age, clinical stage, pathological tumor size, nodes status and estrogen receptor status, all influenced survival (Twelves, Thomson, et al., 1998). Also, they found that the geographical variation in both surgical and non-surgical treatment has a significant effect on variability in survival for women with breast cancer in Scotland. Another population-based study conducted in U.K. discussed the multiple prognostic

factors in breast cancer survival based on their long-term follow-up experience. Researchers focused particularly on the value of histological grade in breast cancer. They used the life-table method to produce survival curves and used the log-rank test to analyze the differences. Researchers found a highly significant correlation between histological grade and prognosis, together with tumor size, lymph node involvement and other factors (Elston, Ellis and Pinder, 1998). Researchers also discussed that reasons why histological grading had not been regarded as an important procedure in routine diagnostic histopathology even though the importance of histological grading and the clear correlation with breast cancer survival had been demonstrated in many studies. Elston, Ellis and Pinder (1998) emphasized that important prognostic factors such as lymph nodes stage, histological grade and pathology tumor size are the basis of the selection of optimum therapy for women with breast cancer.

In summary, there are several possible reasons for the trend of increased incidence rates, decreased mortality rates and increased survival. The major reasons could include birth cohort effects, improvement of treatment, earlier detection of breast cancer, and changes in prognostic factors of breast cancer. In this thesis I have focused on the relationship between adjuvant systemic therapies and breast cancer survival. Many studies on this topic have been based on randomized controlled clinical trials. However, research that follows is a population-based retrospective cohort study using cancer registry data for the patient population in northern Alberta.

Table 2.1 summarizes the studies cited in this literature review.

Table 2.1: Summary of Studies on Breast Cancer Incidence and Mortality.

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
1. Tarone, et al. National Cancer Institute, 1992.	White females in the United States	Retrospective cohort	Nonparametric, permutational analyses	- The divergence in trends with age is shown to be consistent with an increase in breast cancer risk with successive birth cohorts from 1900-1916 and with a decrease in breast cancer risk with successive birth cohorts beginning around 1926.
2. Tarone, et al. National Cancer Institute & Statistics Canada, 1997.	White & black females in the United States, all females in Canada	Retrospective cohort	-Two-sided t tests - Age-period-cohort models - Age-adjusted mortality rate	- For white women, mortality rate was higher in Northeast in the U.S., for black women were not. - A marked moderation of risk by 4-year birth cohorts was found for U.S. white women after 1950, whereas stable or slightly decreasing trends was found for U.S. black women and Canadian women. - The slope of mortality calendar period trend increased in the 1980s compared with 1970s for all women. - 1991-1992, a trend of decreasing mortality rates was found for white women in the U.S. and for Canadian women. **(Table Continued)**

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
3. Chu, et al. National Cancer Institute & National Center of Health Statistics, 1996.	White women in the United States	Retrospective Cohorts	- Linear regression analyses of log-transformed rates -Piecewise regression analyses - Age-adjusted mortality rate - 3-year relative survival rate	- Age-adjusted mortality rate dropped 6.8% from 1989 to 1993 - A significant 2% decrease in mortality rate per year for women age 40-79 - Incidence rates for localized disease increased rapidly from 1982 to 1987, stabilized or increased slowly thereafter for women age 40-79. - 3-year relative survival rates increased steadily and significantly from 1980 to 1989 for all ages.
4. Gaudette, et al. Statistics Canada, 1996.	All women in Canada	Retrospective cohort	- Age-standardized incidence rate - Age-standardized mortality rate - Observed survival by Kaplan-Meier method	- Number of new cases were doubled from 6,900 to 18,600 between 1969 and 1996 - Age-standardized incidence rates rose less rapidly from 78 to 107 per 100,000 population between 1969 and 1996 - Incidence rates increases rapidly for age 30-70, leveled off, and dropped after 84

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
			- Wilcoxon univariate chi-square test	- Number of deaths rose between 1969 and 1996 from 2,750 to 5,300. - Mortality rates remained stable at 30 to 32 per 100,000 between 1969 and 1990 and declined from 31 to 29 per 100,000 the lowest since 1950. - Well-established risk factors: age, country of birth, family history, benign proliferate breast disease, hormonal status, socioeconomic status, obesity and religion - Incidence rates relatively high in BC, MA, SA and NS, and relatively low in QB, NF, Yukon and the Northwest Territories - 5-year observed survival 70% - 10-year observed survival 50%
5. Hermon, et al. Imperial Cancer Research Fund, U.K., 1996.	Women population in 20 western countries	Retrospective cohort	-Age-standardized mortality rate	-Mortality rates increased in earlier decades, more recently begun to decline.

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
			- Log-linear Poisson models	- In most of countries the mortality declines appeared to be due to birth cohort effects and period effects - The decline in mortality in women born after 1920 appeared to be related to a reduction in Childlessness and a reduction in age at first birth those generations. - the recent overall decline in several countries may be due to an increase in survival resulting from improved management and treatment
6. Stockton, et al. Univ. of Cambridge, U.K., 1997.	All women with breast cancer registered by the East Anglian cancer registry between 1982 and 1989	Retrospective study	- 3-year relative survival rate - Cox's proportional hazards	- Stage I & II increased 1.5 times in 1986-9 than 1982-5 - For women age under 65, survival improvement was significant. - High relative survival in women with early stage tumor and poorer in women with Stage III & IV tumor - Increased use of Tamoxifen may be major contributor in the improvement of treatment. **(Table Continued)**

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
7. Brenner, et al. Univ. of Ulm, et al. Germany, 1998.	Women with breast cancer, below age 80, registered in the cancer registry of Saarland	Retrospective study	- Life table method - 5-year absolute survival - 5-year relative survival - Chi-square test	- All age groups combined, absolute survival rates improved from 63.4% in 1980-84 to 68.6% 1990-94. - Survival improvement was more pronounced for age group 50-59 between 1980-84 and 1985-1989, and for age group 60-69 between 1985-89 and 1990-94. - 5-year absolute survival was lowest in age group 70-79. - 5-year relative survival had similar improvement as 5-year absolute survival in the calendar period - 5-year relative survival was lowest in age group 50-59.
8. Adami, et al. Swedish cancer society, Sweden, 1986.	Women diagnosed with breast cancer between 1960 and 1978 in Sweden	Retrospective cohort	- Life table method - 5-year observed survival - 2-year & 5-year relative survival	- 5-year OS increased 8.3% from 1960-64 period to 1975-78 period. - 2-year RS increased from 80.3% to 88.6% and 5-year RS increased from 64.0% to 74.5% from 1960-64 period to 1975-78 period. **(Table Continued)**

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
				- A general trend toward improved RS between each of four successive periods - A significant temporal change for all age groups from age 45 and older
9. Burns, et al. Cross Cancer Institute, Canada, 1979.	All women with breast cancer in northern Alberta in 1971-72	Retrospective cohort	- Observed 5-year survival rate - 5-year relative survival rate - Linear regression	- 5-year relative survival 73% - Women age 40-59 had higher survival rate (79%) than the others, and women age 35-39 had poor survival rate (59%) - 5-year survival rate for perimenopausal women 79%, for pre- & post-menopausal 72% - Survival rate was related to number of lymph nodes and stage.
10. Bonadonna, et al. Istituto Nazionale Tumori, Milan, 1976.	Patient admitted to the Istituto Nazionale Tumori of Milan, Italy	Randomized Clinical Trial	- Life test method - Chi-square test	- Treatment failure occurred 27% in control group and 5.3% in combined chemotherapy group.

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
11. Early Breast Cancer Trialists' Collaborative Group, 1992.	Muli-centered randomized clinical trial	Randomized clinical trial	- Log-rank test - Odds reductions of death or of recurrence	- Highly significant reduction of death and of recurrence produced by tamoxifen and by polychemotherapy - Chemo-endocrine therapy was better than chemo or tamoxifen alone - Absolute improvement in 10-year survival was about twice as great for node-positive patient as for node-negative patient.
12. Early Breast Cancer Trialists' Collaborative Group, 1995.	Muli-centered randomized clinical trial	Meta-analysis	- Log-rank test - Odds reduction	- Recurrence rate for surgery plus radiotherapy was three times lower than that for surgery alone. - No definite difference in 10-year survival
13. Paterson, et al. Cross Cancer Institute, Canada, 1982.	All patients with recurrence, 1963-79, Alberta.	Retrospective study	- 3- & 5-year survival rate	- Chemotherapy might improve short-term survival, but made no difference for long-term survival
14. Paterson, et al. Cross Cancer Institute, Canada, 1985.	All patients with recurrence presented in 1975 onward, northern Alberta.	Retrospective study	Kaplan-Meier method	- Little difference in survival by systemic therapy

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
15. Jacobson, et al. National Cancer Institute, 1995.	National Cancer Institute	Randomized Single-institution trial	- Kaplan Meier method - Overall survival - Disease-free -Mantel- Haenszel test	- 10-year overall survival was 75% for patients treated with mastectomy, and was 77% for patients treated with lumpectomy plus radiation - 10-year disease-free survival was 69% for the former, and was 72% for the latter.
16. Fisher et al. National Surgical Adjuvant Breast and Bowel Project, 1995.	Multi-centered clinical trial, U.S.	Randomized clinical trial	- Chi-square test - Log-rank test -Overall survival - Disease-free survival	- No significant difference in overall and disease-free survival - Cumulative recurrence rate was 35% for patients treated with lumpectomy, was 10% for patients treated with lumpectomy plus irradiation.
17. Arriagada, et al. INSERM, France, 1996.	Conducted at the Institute Gustave Roussy, France.	Randomized clinical trial	- Log-rank test - Cox's proportional hazards model	- No significant difference in overall survival, distant metastasis, contralateral breast cancer, new primary malignancy, and local recurrence rate between the two surgical groups, or between lymph node irradiation groups.

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
18. Henderson, et al. UCSF Cancer Center, U.S., 1994.		An overview of randomized clinical trials		- At 10 years, the survival difference between treated and control patients for premenopausal women with positive nodes, chemotherapy will be 12% for disease free survival, and 10% for overall survival. - At 10 years, the survival difference between treated and control patients for postmenopausal women with positive nodes, tamoxifen will be 9% for disease free survival, and 7% for overall survival.
19. Olivotto, et al. British Columbia Cancer Agency, 1994.	All women with breast cancer diagnosed in B.C. between 1974 and 1984	Retrospective cohort study	- Overall survival - Disease specific survival - Kaplan Meier Method - Log-rank test	- 7-year overall survival for women age 50-89 was 53.9% and 58.3% in 1980 and 1984 respectively, and 7-year disease-free survival was 62.5% and 70.4% respectively. - 7-year disease-specific survival for women age less than 50 was 65.2% and 76.3% in 1974 and 1984 respectively, and 7-year disease-free survival was 64.8% and 74.6% respectively.
20. Fletcher, et al. National Cancer Institute, 1993.		Randomized control trial (meta-analysis)	- Relative risk - Mortality reduction	- For women age 50-69, morality reductions were about 30% in two trials significantly, and for women age 40-49, mortality decreased about 13% not significantly.

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
21. Kopans, et al. Harvard Medical School, 1994.		An overview of RCTs		- Suggested that women 40-49 can benefit from screening just as can women age 50-59.
22. Byrne, et al. National Cancer Institute, 1994.	Population-based, world-wide screening	Screening program	Retrospective cohort study	- Overall, stage I had survival 43.9% advantage than stage III. - mammography detected 34.6% cases (survival 90.9%), physical exam and mammography detected 32.2% cases (survival 79.0%), physical exam detected 4.7% cases (survival 88.2%)
23. Barchielli, et al. Center for the Study and Prevention of Cancer, et al. Italy, 1994.	Women with invasive breast cancer survival in Florence, Italy.	Retrospective cohort study	- Kaplan Meier method - 5-year relative survival - Cox model	- Observed 5-year survival 68.3% - 5-year survival 75.4%
24. Thurfjell, et al., Univ. Hospital, Sweden. 1996.	Population-based mammographic screening		- Cumulative survival - x^2 test	- For all women, 7-year cumulative survival 88%, for younger women it was 92%, and for women older than 50 it was 87%.

(Table Continued)

Author, Institute & Date	Study Population & Site	Study Type	Statistical Method	Study Results
25. Twelves, et al. The Scottish Breast Cancer Focus Group, U.K., 1998.	All women with breast cancer, registered in the Scottish Cancer Registry between 1987 and 1993.	Retrospective study	- Kaplan Meier survival estimate - Cox PH model	- Age, clinical stage, pathological tumor size, nodes status and estrogen receptor all influenced survival. - Geographical variation in surgical treatment had significant effect on survival.
26. Elston, et al. Dept. of Histopathology, City Hospital, Nottingham, U.K., 1991.	Population-based study	Retrospective cohort study	- Life table method - Log-rank test	- Histological grade had very strong correlation with survival

CHAPTER 3

METHODS

Study Goals

1. What are the survival rates of women with breast cancer in Northern Alberta diagnosed during 1971-73, 1974-76, 1977-79, 1980-82, 1983-85, 1986-89?

Questions related to goal 1:

(1) What is the overall (1-year, 3-year, 5-year, 10-year) survival rate for women in Northern Alberta diagnosed with breast cancer between 1971 and 1989 and registered in the Northern Alberta Registry?

(2) What are the survival rates by diagnosis period in Northern Alberta?

(3) What are the survival rates by age over time in Northern Alberta?

(4) What are the survival rates of patients with or without systemic adjuvant therapy?

2. Are changes in survival related to changes in the use of systemic adjuvant therapy in breast cancer?

Question related to goal 2:

How is survival related to systemic adjuvant therapy after adjusting for clinical prognostic factors including age, stage, tumor size, histological grade, menopausal status, hormone receptor level, radiotherapy and type of surgery?

It is hypothesized that the survival rate has improved subsequent to the introduction of systemic adjuvant therapy after adjusting for age, stage, tumor size, histological grade, menopausal status, hormone receptor level, radiotherapy, surgery.

Study Design

This study is a population-based, retrospective, cohort study of breast cancer survival in women with breast cancer in northern Alberta. Data are from both the Alberta Cancer Registry (ACR) and the Northern Alberta Breast Cancer Registry (NABCR) collected between 1971 and 1989. The analyses include a series of descriptive studies of breast cancer incidence and survival, and statistical modeling of predictors of breast cancer survival. The SAS (version 6.12) software in a Unix environment was used in statistical analyses.

Study Population

The target population includes all patients with breast cancer resident in the northern Alberta who were registered in the Northern Alberta Breast Cancer Registry between 1971 and 1989. Northern Alberta is defined as all areas in the province north of Red Deer. At least 80 percent of women diagnosed with breast cancer in northern Alberta are registered on the Northern Alberta Breast Cancer Registry. All patients had been

followed after diagnosis until November 25, 1998. During the time that subjects were followed, subjects (censored) sometimes were lost to follow up, or subjects (noncensored) completed the study. The follow up period was from 7 years to 27 years long.

Data Sources

The study used data for patients registered in the NABCR between 1971 and 1989. The information in the database has been supplemented with information from the ACR.

The Northern Alberta Breast Cancer Registry (NABCR) collected information on breast cancer cases registered between 1971 and 1989 and reported to Cross Cancer Institute. The NABCR contains detailed information of breast cancer cases and includes patients' personal information and family history, details of primary diagnosis, pathological information, treatment of primary breast cancer, follow-up information, records and treatment of local and regional recurrence, and information about distant metastases. This database includes 7942 cases in total.

The Alberta Cancer Registry (ACR) registers all cancer cases that have been diagnosed in Alberta with malignant tumors (in situ as well as invasive) and contains identifying information, details of diagnosis, treatment, and cause of death. The information entered into the registry is abstracted from various documents, which are maintained in the patient's medical record, including the discharge summary, progress

notes, pathology reports and surgery reports. The Alberta Cancer Registry along with the registries in the other 9 provinces and 2 territories contribute data to the National Cancer Incidence Reporting System Operated by Statistics Canada, which produces national cancer statistics.

Study Subjects

Inclusion Criteria:

1. Breast cancer cases with information both in the Northern Alberta Breast Cancer Registry and in the Alberta Cancer Registry.
2. Female.
3. Resident of Alberta at the time of diagnosis.

   Non-residents of Alberta at the time of diagnosis may not have complete study data.
4. First breast cancer was diagnosed in Alberta between January 1, 1971 and December 31, 1989 and who had not had a previous cancer diagnosis except non- melanoma skin cancer and/or cervical in situ cancer.

   This criterion was chosen to avoid the effect on survival of other cancers (non-melanoma skin cancer or cervical cancer in situ are very rarely fatal).

Data Definitions

Two variables were used as identifiers for data merging: the Alberta Cancer Board (ACB) number and malignancy number. The ACB number is contained both in ACR and NABCR databases. Malignancy number is contained only in ACR database.

ACB Number: uniquely identifies a client of an Alberta Cancer Board facility and appears on the patient's paper medical chart/microfiche, which is assigned to a client at his/her first contact with the ACB. This number does not change, even when patients attend another ACB-clinic.

Malignancy Number: identifies the chronological order of each diagnosed cancer. This also allows the linking of information on a particular cancer to that record number and differentiation between multiple malignancies. If the order of the primaries changes, the primary numbers have to be changed to reflect the correct time sequence, as determined by the date of diagnosis of the primary tumors.

Treatment Type: records the methods used to treat the primary site and the treatment must be received before it can be recorded.

According to the model building strategies (Please refer to "Statistical Methods" in this chapter), any variable, which was biologically and clinically associated with breast cancer treatment and survival, should be included in the model building. For instance, age and diagnosis time contained some important information related to patient, her breast cancer and survival afterwards; adjuvant chemo, hormone and radiotherapy were the major interest of the study. Therefore, these five variables were included in the model building. Besides these elements, other risk factors were also considered as possible variables of the model. For each variable, both the cause specific survival and relative survival had been calculated to look at the survival differences among the subgroups.

1. Age

All patients were categorized into one of five age groups:

Age group 1: under 40 years of age

Age group 2: equal or older than 40 years of age and under age 50

Age group 3: equal or older than 50 years of age and under age 60

Age group 4: equal or older than 60 years of age and under age 70

Age group 5: equal or older than 70 years of age

2. Adjuvant Therapy

i) **No Adjuvant Therapy Group**

ii) **Single Therapy Groups:** a) Chemotherapy group

b) Hormonal therapy group

c) Radiotherapy group

iii) **Multiple Therapy Groups:** a) Radio-Hormone therapy group

b) Radio-Chemo therapy group

c) Chemo-Hormone therapy group

3. Diagnosis Period

For the total 19 years of data collection, the 6130 breast cancer patients were divided into 6 diagnostic period categories. Each diagnosis period included 3 continuous calendar years starting from 1971 to the end of 1989 (1971-73, 1974-76, 1977-79, 1980-82, 1983-85, 1986-89). Only the last diagnosis period included 4 continued calendar years from 1986 to 1989.

4. Surgery

Surgery is the primary treatment of breast cancer after diagnosis. Patients who received adjuvant treatments are usually given surgical treatment first. Patients who received no primary surgery usually had very small early stage tumors, or had breast cancers that already metastasized. There were very few patients with tiny tumors in this study. Therefore, "surgery" contained two subgroups, those receiving surgery and those not receiving surgery.

5. Clinical Stage

Stage is a very important determinant of breast cancer survival. Clinical stage was considered as a variable rather than pathological stage since the data on clinical stage were much more likely to be completed than the data on pathological stage. According to the standard classification of clinical staging, breast cancers were classified into four clinical stages when data were initially collected in this study.

6. & 7. Tumor Size & Lymph Node

Tumor size and lymph node are associated with the prognosis of breast cancer. Theoretically, patients with small tumors and negative lymph nodes have better survival comparing with those with large tumors and positive lymph nodes. The variable of tumor size was categorized into three groups based on the diameter of the tumor: 0-2 centimeter, 2-5 centimeter, and >5 centimeter. The variable lymph node contained two subgroups, nodes negative and nodes positive.

8. Estrogen Receptor & Progestogen Receptor

Estrogen receptor is an indication of hormone treatment. Patients with positive estrogen receptors should sustain better outcomes with hormone treatment.

9. & 10. Morphology Type & Histology Grade

Morphology type and histology grade provide pathology information of breast cancer. The classification of breast cancer in morphology or histology is not only the evidence of diagnosis but also a predictor of prognosis. Patients in this study were categorized into three groups based on the morphological type of their breast cancer: Ductular, Lobular, and Other. Moreover, patients were grouped into three levels according to the histology grade of their breast cancers, which were grade I, grade II, and grade III.

11. Menopausal Status

Menopausal status reflects a patient's physiological status, which is related to patient's age at diagnosis, breast cancer treatment and survival.

Outcome Measurements for Goal 1

Survival after the diagnosis of breast cancer is measured in three ways: the observed (overall) survival rate, the cause-specific survival rate and the relative survival rate. These rates have been calculated based on the deaths occurring within 1 year, 3 years, 5 years and 10 years of diagnosis.

Observed (Overall) Survival:

The most basic measure of the survival of patients with breast cancer is the observed survival rate for time period of interest. This is calculated by dividing the total number of survivors within the time period of interest after the date of diagnosis by the

total number of patients diagnosed with breast cancer adjusting for lost to follow up. The observed survival rate is not a particularly useful measure for making comparisons between patient groups since not all deaths will be due to the breast cancer.

Cause-Specific Survival:

Cause-Specific survival rate is calculated from the total number of survivors from breast cancer after diagnosis for a time period of interest divided by the total number of patients diagnosed with breast cancer adjusting for lost to follow up. The cause-specific survival rate only counts those deaths that are attributed to breast cancer, while all other deaths are treated as censored. Therefore, the cause-specific survival rate can be used to estimate the probability of surviving breast cancer, independent of mortality due to competing risks.

Relative Survival Rate:

The relative survival rate is defined as the observed survival rate in the patient group divided by the expected survival of a comparable group from the general population. One advantage of this measure is that information on cause of death is not required, thereby circumventing problems with the inaccuracy or availability of cause of death information. Relative survival rate has become the preferred measure for the analysis of patient survival calculated from population-based cancer registries. A relative survival rate equal to 1 indicates that during the specified time interval, mortality in the patient group was equivalent to that of the general population. The attainment and

maintenance of a relative survival rate of 1 indicates that there is no excess mortality due to breast cancer and the patients are assumed to be 'cured'.

The relative survival rates were also calculated for patients with each prognostic factor of interest for this study compared with their cause specific survival rates. These factors included diagnosis period, age, single adjuvant therapy and multiple adjuvant therapy. See the "Data Definitions" section for how sub-groups of each factor were categorized.

Statistical Methods

Goal 1

The Kaplan-Meier method was used to do a series of descriptive analyses. The observed (overall) and cause-specific survival rates were calculated. Moreover, the survival rates over time by age group and by adjuvant therapy were calculated. The trends in survival over time by time cohort were observed. Thus the following analyses were performed.

Questions and analyses related to goal 1:

(1) What is the overall (1-year, 3-year, 5-year, 10-year) survival rate for women in Northern Alberta diagnosed with breast cancer between 1971 to 1989 and registered in the Northern Alberta Registry?

a. Calculate overall survival rates (1-year, 3-year, 5-year, 10-year) and 95% CI.

b. Calculate cause-specific survival rates (1-year, 3-year, 5-year, 10-year) and 95% CI.

(2) What are the survival rates by diagnosis period in Northern Alberta?

Calculate cause-specific survival rates by diagnosis time. All patients were divided into 6 diagnosis time groups.

(3) What are the survival rates by age over time in Northern Alberta?

Calculate cause-specific survival rates by age group over time. All patients were divided into five groups.

(4) What are the survival rates of patients with or without systemic adjuvant therapy?

Calculated cause-specific survival rates by adjuvant therapy over time. All patients were divided into 3 major groups.

The log-rank test was used to examine the survival differences between pairs of subgroups for all defined variables. A two-tailed test was used with the significance level of 0.05.

The relative survival rates were calculated using the SAS SURV2 software application. The relative survival rates were calculated corresponding to the cause-specific survival rates, which include 1-year, 3-year, 5-year and 10-year relative survival rates. Also, the relative survival rates were calculated by age, adjuvant therapy and diagnosis time. The relative survival rate is a ratio of the observed survival rate of the breast cancer patient population divided by the expected survival rate in the Canadian general population. The general population mortality parameter was obtained from life table published by Statistics Canada between 1970 and 1990.

Goal 2

Questions and analyses related to goal 2:

How is survival related to systemic adjuvant therapy after adjusting for clinical prognostic factors including age, stage, tumor size, histological grade, menopausal status, hormone receptor level, radiotherapy and type of surgery?

Cox Model

The chosen methods must account for both censored and uncensored observations. The Cox's regression model allows uncompleted data, which is almost always happens in the study of survival analysis. The Cox proportional hazards model assumes a parametric form of the effects of the independent variables and it allows an unspecified form for the underlying survivor function. The formula for the Cox PH Model is:

$$h(t, \mathbf{X}) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

This model gives an expression for the hazard at time t for an individual with a given specification of a set of independent variables denoted by **X**. The **X** represents a collection of predictor variables that is being modeled to predict an individual's hazard. The hazard at time t is the product of two quantities. The h_0 (t) is the baseline hazard function. The second quantity is the exponential expression e to the linear sum of $\beta_i X_i$, where the sum is over the p independent X variables.

1) Variable Selection

The independent variables were identified before the actual steps of building the Cox model. To identify the independent variables, treatments of interest and risk factors of breast cancer survival were taken into account. The treatments of interest were based on the primary surgery and adjuvant therapies including chemo, hormone and radiotherapy. The adjuvant therapies were the major interest of this study. The risk factors, which were associated with breast cancer survival biologically (such as age) or clinically (such as clinical stage), were also considered as possible independent variables for the model building. The strategies of identifying these risk factors were to calculate

both cause specific survival and relative survival, and to see if there is any difference in survival among the subgroups of each risk factor. A primary condition was that these risk factors should have been categorized in a biologically and clinically meaningful way. If there were significant differences among the subgroups of a risk factor in survival, it was inferred that patients varying in a known risk factor might have different influences on the effect of systemic therapy, as they may affect and/or explain any observed effect. Then, it was selected as a possible independent variable for the model building.

2) Model Building

The stepwise method was employed as the model building strategy. Variables are entered into and removed from the model in such a way that each forward selection step may be followed by one or more backward elimination steps. If variables achieve p-values of ≤ 0.10 in the analysis of the main effect they were entered into the model.

CHAPTER 4

DATA MERGING

The data merging was based on two data sources of Alberta Cancer Registry and the Northern Alberta Breast Cancer Registry.

A simple example is shown below as to how ACB records the occurrences and treatments for a patient with multiple primary cancers (e.g. breast cancer and another kind of cancer). For instance, a patient had a primary lung cancer before she had primary breast cancer. The malignancy number was recorded as 1 for lung cancer. Because the patient received radiotherapy first and then chemotherapy after that, radiotherapy for lung cancer was entered first and chemotherapy for lung cancer was entered second in the patient's file in ACR. The patient then developed a primary breast cancer. Therefore, the malignancy number was recorded as 2 for breast cancer. She received treatment of surgery for breast cancer first and chemotherapy afterwards. Therefore, surgery for breast cancer was entered as the third treatment, chemotherapy for breast cancer as the fourth treatment in the patient's file in ACR. Therefore, the patient has four records for her cancers and treatments, and the ACB number was the same in all the records.

ACB_NO	Cancer	MAL_NO	Treatment	Observations
x123456	Lung	1	radio-	1
x123456	Lung	1	chemo-	2
x123456	Breast	2	surgery	3
x123456	Breast	2	chemo-	4

Data Merging Steps

The step taken to select eligible patients is shown in Table 2. The final study sample consisted of 5483 patients with only one breast cancer, 393 patients with only two breast cancers, 394 patients with breast cancer and non-melanoma skin cancer and 84 patients with breast cancer and cervical in situ cancer g. Giving a total of 6354 patients included in the statistical analyses.

Step1: I merged the information of 7942 breast cancer cases contained in NABCR with the information of these same cases contained in ACR according to the unique ACB number. and malignancy number. I found that 26 cases had no information in ACR. Therefore, these cases were excluded from this study and 7916 cases were left.

Step2: I excluded 48 male cases and 7868 cases were left.

Step3: I selected 7193 cases that as least had one breast cancer diagnosed in Alberta between 1971 and 1989, at the same time patients were residing in Alberta.

Step4: I identified 5483 cases with only one breast cancer and without other cancers.

Step5: I identified 1710 cases with multiple cancers including at least one breast cancer.

Step6: I identified 1307 cases that had the other cancer(s) besides breast cancer.

Step7: I selected 430 cases without other cancers except for breast cancers from 1307 cases obtained from step6 and left 393 cases that had a first breast cancer diagnosed in Alberta between 1971 and 1989 to be used for statistical analysis of this study.

Step8: I identified 478 cases with non-melanoma skin cancer from 1307 cases that had the other cancer(s) except for breast cancer, then, excluded cases with cancer(s) other

than breast cancer and non-melanoma skin cancer. There were in total 394 cases to be used for statistical analysis of this study whose first breast cancers were diagnosed in Alberta between 1971 and 1989.

Step9: I identified 98 cases with cervical in situ cancer from 1307 cases that had the other cancers except for breast cancer, then, excluded cases with cancers other than breast cancer and cervical in situ cancer. There were totally 84 cases to be used for statistical analysis of this study whose first breast cancer was diagnosed in Alberta between 1971 and 1989.

Step10: I merged the cases obtained from step4 (5483), step7 (393), step8 (394), and step (84) to compose a whole data set used in this study, in which all cases met the inclusion criteria.

CHAPTER 5

CHECKING FOR DATA QUALITY

The purpose of data quality checking was to correct or reduce the inconsistency of data between the two registry databases for all variables common to both, which were used in this study. Where inconsistencies were observed chart review was undertaken. The type of the records used in the chart review included paper charts and fiches, which were provided by the Alberta Cancer Board.

The data quality checking was based on merging of the Alberta Cancer Registry (ACR) Northern Alberta Breast Cancer Registry (NABCR) databases. The Alberta Cancer Registry records identifying information such as patient's name, date of birth and sex. The ACB-number is a unique identifier for each case, assigned by the ACR. The Northern Alberta Breast Cancer Registry is an extended registry recording information on all breast cancer cases diagnosed between 1971 and 1989 that is maintained by the Breast Cancer Tumor Group of the ACR. The NABCR was designed to capture a more complete set of data on breast cancer cases than the ACR, and is a complement to ACR.

The consistency of all mutual variables relevant to the study in the ACR and in the NABCR was checked including date of birth, date of death, date of diagnosis and cause of death. In the procedure of the data quality checking, for the date of birth, date of death and date of diagnosis, the records of the two databases were mostly consistent. However, for cause of death, it was found that the records between ACR and the NABCR were not consistent in 152 cases. For some of them, the evidence of cause of death could not be discovered by chart review.

The checking procedure was started from date of birth. In total, it was found that in 116 cases the records between ACR and the NABCR were not consistent. Cases were reviewed, in which the difference of date of birth is more than two years (57 cases) between the two datasets. There were 36 patients whose records were checked based on charts and there were other 21 patients whose medical records were maintained as fiches that contained exactly the same information as the original charts (we call both of these sources of data 'chart' later in this article).

During the procedure of chart review, some problems were found in the original charts. Firstly, the original records in the chart were not consistent for date of birth as they came from different hospitals. Secondly, the date format used in the chart was not the same and each registry chose a different one entered in the computer. For instance, the date format 19/04/22, was recorded as a patient's date of birth in the chart. One registry took 19 as the year of birth, therefore, the patient's date of birth was considered as 1919. However, another registry took 22 as the year of birth, therefore, it was regarded that the patient was born in 1922. Thirdly, the original chart did not maintain the patient personal information completely (e.g. only has patient's age, but no birthday), or some script in the chart (especially in some fiches) was not clear, or some pages of the chart were lost. For example, if only the patient's age was found in the chart, in this circumstance, the date of birth was inferred form the patient's age and the date of the record. However, some women hide their age or birthday intentionally years after the first clinic visit.. It may be difficult to find out that which record was correct.

Chart review procedure was based on following steps: Firstly, if only one record of date of birth could be found in a chart or fiche, this one was chosen. Secondly, if both

types were found in the chart, the progress notes were referred to, or the earliest record was taken, or a reasonable record was taken if the records from different hospitals did not match. The date of birth in ACR was used for 21 cases in this study among a total of 57 cases. The date of birth in NABCR was used for 35 cases in this study. There was one case in which the birth date was found in the fiche that was neither the date in ACR nor the date in NABCR.

The second variable that was checked was the date of death. It was found that the consistency of date of death between the two registries was very satisfactory (96.6%). There were only four patients whose dates of death were not consistent. The date of death in the ACR was taken for each patient based on the date appearing on the death certificate in the chart.

The third variable that was checked was the date of diagnosis. The variables of anniversary date (year, month, and day) in the NABCR provided similar information to the variable of date of diagnosis in the ACR provided. However, the anniversary date actually provided the date of patient receiving treatment. Theoretically, treatment date should have been late than diagnosis date. We reviewed all charts whose treatment date was more than 1 year later than diagnosis date. In total eleven charts were reviewed. For patients with more than one primary breast cancers, the first primary breast cancer was checked. Ten of them had only one primary breast cancer. One of them had two primaries. These eleven cases were in either of the following two categories: 1. The anniversary date was two years later than the diagnosis date, 2. The anniversary date was earlier than the diagnosis date. Chart review for the variable date of diagnosis was based on the date issued in pathological report. The NABCR's anniversary year was taken as

the year of diagnosis in 7 cases and ACR's was taken as the correct date of diagnosis in 4 cases.

The last variable checked was cause of death. Four types of document were referred to in the review procedure including the autopsy report, the standard death certificate coded according to the International Classification of Diseases 9th edition, the extracted document from the standard death certificate, and a hand-written record of death. Cause of death was considered unknown if above documents could not be found. In 152 cases the cause of death recorded in ACR did not agree with the cause of death recorded in NABCR. In 49 cases, the cause of death was not recorded in NABCR, but it was recorded as breast cancer in ACR. Therefore, the cause of death in ACR was taken since ACR had a longer follow-up record. Mostly, this group of patients died after 1989. In these cases, the charts were not reviewed. Moreover, fifty-seven patients' death was due to primary breast cancer according to the NABCR. However, in the ACR it was recorded as cause unknown or another cause of death. This occurred usually when a patient had metastases and had died according to the record in the chart, without an autopsy report or death certificate being found. A rare circumstance was that patient was still alive but was recorded dead. There were in total 46 cases in which the cause of death was breast cancer in the ACR, but the cause of death was another cancer, or other than cancer in the NABCR. A common finding was that carcinoma of breast cancer was recorded as the secondary cause of death and primary cause of death was another cause (e.g. Bronchopneumonia) even though the patient had metastases. Therefore, it might be more reasonable if the primary cause of death was recorded considered as breast

carcinoma. However, we kept the cause of death as it is showed in the death certificate. In some cases, doctors did not record the primary cause of death clearly in the charts.

Both the ACR and the NABCR contained some errors in certain variables. The record review provided useful data for the study and also it provided evidence of the need for improvement of data quality in both two registries.

CHAPTER 6

RESULTS

Section 1: Overall and Cause Specific Survival Rates

1. Overall Survival Rate (Table 6.1)

The Kaplan-Meier method was used to calculate the survival rates based on the data set (including 6130 patients) for statistical analysis. The overall 1-year survival rate was 94.0% for breast cancer patients in the Northern Alberta. The survival rate decreased to 78.4% at three years after diagnosis, 67.5% at the 5^{th} year and 51.3% at the 10^{th} year. Although overall survival in the Kaplan-Meier curve showed that the slope sharply decreased during first 3 years, the slope decreased more gradually in the next following years.

2. Cause Specific Survival Rate for All Patients (Table 6.1)

The 1-year cause specific survival rate was 95.5% for breast cancer patients diagnosed between 1971 and 1989 in the Northern Alberta. The 3-year cause specific survival rate was 82.6%. The 5-year survival rate was 73.3% and 10-year survival rate was 60.5% .for women with breast cancer. The survival curves for cause specific survival as well as overall survival rate were the same shape. However, the cause specific survival rate was higher compared with the overall survival rate at each particular year.

3. Cause Specific Survival Rate by Diagnosis Period (Table 6.2)

There was no significant difference or improvement in cause specific survival rate in the early diagnosis period groups (before the diagnosis period of 1983-85). However, the cause specific survival rate of the 1986-89 diagnosis period group indicated statistically significant improvement compared with the other five time period groups. The 1-year cause specific survival rate was 95.9% for patients with breast cancer diagnosed between 1986 and 1989. The cause specific survival rate was 85.6% at 3rd year. It was 77.5% at 5th year and was 66.5% 10th year. Those cause specific survival rates were also higher than the overall survival rates for total diagnosed patients at each observed year. The cause specific survival rate was stratified by clinical stage. The log-rank test indicated that there were significant differences among the subgroups of diagnosis period for patients in stage II or stage III. No significant difference was observed among subgroups of diagnosis period for patients with stage I or stage IV cancers.

4. Cause Specific Survival Rate by Age Group (Table 6.3, Figure 6.1)

Among all age groups patients aged 40 to 49 years had the highest cause specific survival rate. For this group, the 1-year survival rate was 97.7%, 3-year survival rate was 85.9%, 5-year survival rate was 76.8% and 10-year survival rate was 65.2%. The log-rank test indicated that the advantage of survival presented in age group 40-49 years was significant compared with age less than 40 group, age 60-69 group and age 70 plus group. Age less than 40 group and age 70 plus group had relatively lower survival rate among all of age groups. Age 70 plus group had the lowest survival rate at the first three years compared with patients diagnosed with breast cancer at the same time in the other

age groups while the 1-year survival was 94.9% for patients diagnosed at age of 70 years plus, 3-year survival rate was 77.9%. But women below age of 40 years had the lowest survival rate among all age groups 3 years after diagnosis. The 1-year survival rate was 92.5% for women below the age of 40. It was 80.4% for 3-year survival in this group. It was 71.3% at 5 years and was 58.2% at 10 years. The log-rank test showed that there was significant difference between age less than 40 group and age 40-49 group. The difference between age less than 40 group and age 50-59 group was significant too.

5. Cause Specific Survival for Patients Treated with No or Single Adjuvant Therapy (Figure 6.2)

At the end of first year, there was little difference in survival rate between the four groups. Except for the first year, the chemotherapy group had the lowest survival rate among all therapy groups. The 3-year, 5-year and 10-year survivals for the chemotherapy group were 81.5%, 67.7% and 53.8% respectively. The difference between the chemotherapy group and the other groups was significant. Also, the no-adjuvant therapy group had significant differences in survival rates compared with the other three therapy groups. The no-adjuvant therapy group had the lowest survival rates (97.8%) at the end of first year of diagnosis. After the first three years of diagnosis, the "no-adjuvant therapy" group had better survival than the other therapy groups in the following years where the survival rate was much higher than the chemotherapy group. The 5-year and 10-year survival for the no-adjuvant therapy group was 82.0% and 70.5%. There was no significant difference in survival between hormone therapy group and radiotherapy group. Moreover, there was no notable difference in survival between each two groups if

therapy groups were stratified by clinical stage, except that the survival in chemotherapy group was significantly different from no therapy group for stage I and stage II patients.

6. Cause Specific Survival for Patients Treated with or without Multiple Therapies (Figure 6.3)

The no-adjuvant therapy group had better survival than the three combined therapy groups after the fourth year of diagnosis. The radio-chemo group had the worst survival. However, the survival differences among these groups were not significant. There was no significant difference in survival between chemo-hormone and radio-hormone therapy group.

If the groups were stratified by stage, radio-chemo group had significant difference from no therapy group for both stage I and stage II patients. In addition, there was a significant difference between radio-chemo and radio-hormone therapy group for stage II patients.

Section 2: Relative Survival Rates

The results showed that 1-year relative survival rate was 95.7% (95% CI: 95.1%, 96.3%), 3-year relative survival rate was 82.8% (95% CI: 81.7%, 83.9%), 5-year survival rate was 74.2% (95% CI: 72.9%, 75.5%) and 10-year relative survival rate was 62.8% (95% CI: 61.2%, 64.3%) (Table 6.1, Figure 6.4). The relative survival rate for patients diagnosed between 1986 and 1989 was much higher than that of patients diagnosed in the other periods (Table 6.4, Figure 6.5).

Patients between the ages of 40 and 49 years still had better survival rates than those in the other age groups. Patients less than 40 years of age had the worst relative survival among all age groups. There was little difference in relative survival between age 50-59 group of the age 60-69 group. However, age 70+ group had a much better relative survival than the other groups after 3 years of diagnosis (Table 6.5, Figure 6.6).

Comparing patients that received single adjuvant treatment to patients that received no adjuvant treatment, the no adjuvant therapy group had no significant advantage in relative survival to the hormone or radiotherapy group during first 5 years after diagnosis. Actually, women in the hormone therapy group had a slightly better survival rate the end of the first 3 years after diagnosis than radiotherapy and no therapy group. After 5 years of diagnosis, no adjuvant therapy group had a higher survival rate than all therapy groups. Chemotherapy had the lowest relative survival among all groups (Figure 6.7).

Although the no-adjuvant therapy group had the best relative survival rate among all groups, the advantage was not much. Women in the radio-hormone therapy group had a relative survival rate very close to the no adjuvant therapy group in each study year. Women in the chemo-hormone group had a lower relative survival than no adjuvant therapy or radio-hormone therapy group after the first year of diagnosis. However, women in the radio-chemo therapy group had much lower relative survival rate than the other three groups after the first year of diagnosis. (Figure 6.8)

Table 6.1 Overall, Cause-specific and Relative Survival, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 Year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Over All	.9398 (.9339, .9458)	.7837 (.7734, .7940)	.6752 (.6635, .6870)	.5127 (.5001, .5252)
Cause-specific	.9554 (.9502, .9606)	.8257 (.8161, .8354)	.7325 (.7212, .7438)	.6054 (.5926, .6181)
Relative Survival	.9567 (.9505, .9629)	.8279 (.8168, .8390)	.7416 (.7285, .7547)	.6277 (.6120, .6434)

Table 6.2 Cause-specific Survival by Diagnosis Time, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
71-73	.9548 (.9390, .9706)	.8501 (.8225, .8778)	.7599 (.7263, .7936)	.6037 (.5643, .6431)
74-76	.9481 (.9331, .9630)	.8169 (.7907 .8432)	.7165 (.6857, .7473)	.5893 (.5550, 6233)
77-79	.9446 (.9290, .9601)	.7165 (.6857, .7473)	.7056 (.6740, .7372)	.5760 (.5411, .6109)
80-82	.9564 (.9432, .9696)	.8024 (.7764, .8283)	.6990 (.6689, .7291)	.5808 (.5480, .6136)
83-85	.9623 (.9515, .9731)	.8218 (.7980, .8421)	.7145 (.6883, .7406)	.5733 (.5441, .6025)
86-89	.9594 (.9498, .9690)	.8558 (.8386, .8730)	.7748 (.7542, .7954)	.6645 (.6408, .6882)

Table 6.3 Cause-specific Survival by Age Group, Breast Cancer Patients, Northern Alberta, 1971-1989

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
<=40	.9488 (.9318, .9658)	.7787 (.7467, .8109)	.6828 (.6467, .7188)	.5476 (.5089, .5863)
40-49	.9767 (.9685, .9850)	.8591 (.8400, .8781)	.7678 (.7447, .7910)	.6520 (.6258, .6782)
50-59	.9678 (.9588, .9769)	.8304 (.8110, .8498)	.7372 (.7144, .7599)	.6193 (.5988, .6401)
60-69	.9543 (.9431, .9654)	.8319 (.8118, .8519)	.7366 (.7128, .7603)	.5906 (.5636, .6175)
70+	.9248 (.9107, .9390)	.8043 (.7823, .8263)	.7133 (.6876, .7391)	.5823 (.5520, .6126)

Table 6.4 Relative Survival for the Subgroups of Diagnosis Time, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
71-73	.9463 (.9261, .9665)	.8207 (.7866, .8548)	.7319 (.6918, .7720)	.5987 (.5514, .6460)
74-76	.9566 (.9399, .9733)	.8300 (.8002 .8598)	.7360 (.7005, .7715)	.6170 (.5752, 6588)
77-79	.9486 (.9308, .9664)	.7844 (.7525, .8163)	.7109 (.6748, .7470)	.5925 (.5506, .6344)
80-82	.9598 (.9445, .9751)	.8096 (.7806, .8386)	.7142 (.6808, .7476)	.6041 (.5644, .6438)
83-85	.9616 (.9482, .9750)	.8185 (.7931, .8439)	.7165 (.6863, .7467)	.6014 (.5659, .6369)
86-89	.9600 (.9483, .9717)	.8694 (.8494, .8894)	.7983 (.7740, .8226)	.6977 (.6673, .7281)

Table 6.5 Relative Survival for the Subgroups of Age, Breast Cancer Patients, Northern Alberta, 1971-1989

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
<=40	.9466 (.9287, .9645)	.7758 (.7427, .8089)	.6747 (.6375, .7119)	.5427 (.5029, .5825)
40-49	.9767 (.9679, .9855)	.8546 (.8345, .8747)	.7641 (.7398, .7884)	.6559 (.6282, .6836)
50-59	.9663 (.9561, .9765)	.8266 (.8058, .8474)	.7375 (.7131, .7619)	.6282 (.6003, 6561)
60-69	.9576 (.9452, .9700)	.8374 (.8150, .8598)	.7488 (.7219, .7757)	.6222 (.5894, .6550)
70+	.9301 (.9112, .9490)	.8180 (.7875, .8485)	.7528 (.7153, .7903)	.6658 (.6119, .7197)

Figure 6.1: Cause-specific Survival Stratified by Age Group, Breast Cancer Patients, Northern Alberta, 1971-1989.

Figure 6.2: Cause-specific Survival Stratified by Single Adjuvant Therapy, Breast Cancer Patients, Northern Alberta, 1971-1989.

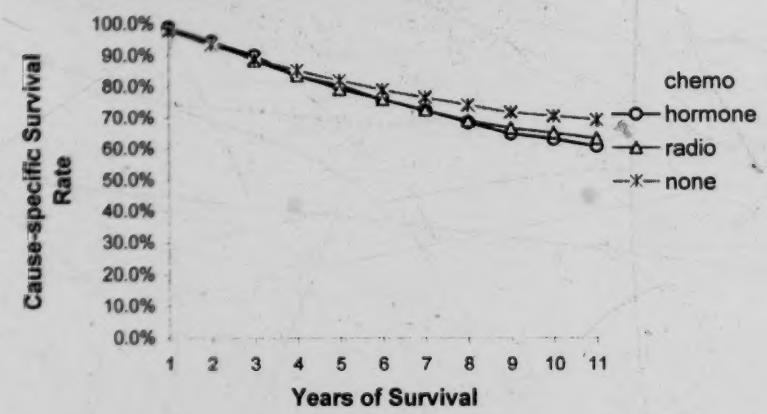


Figure 6.3: Cause-specific Survival Stratified by Multiple Adjuvant Therapies, Breast Cancer Patients, Northern Alberta, 1971-1989.

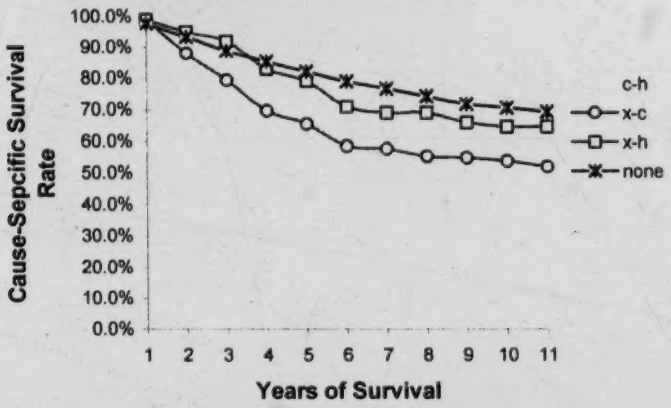


Figure 6.4: Compare Over All, Cause-specific and Relative Survival, Breast Cancer Patients, Northern Alberta, 1971-1989.

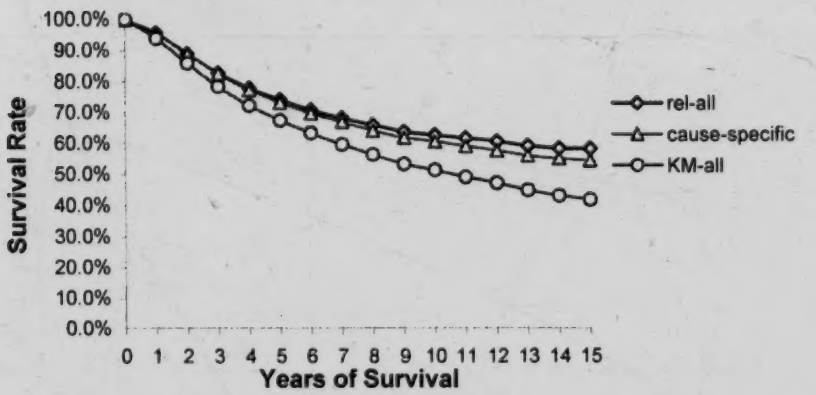


Figure 6.5: Relative Survival by Time of Diagnosis, Breast Cancer Patients, Northern Alberta, 1971-1989.

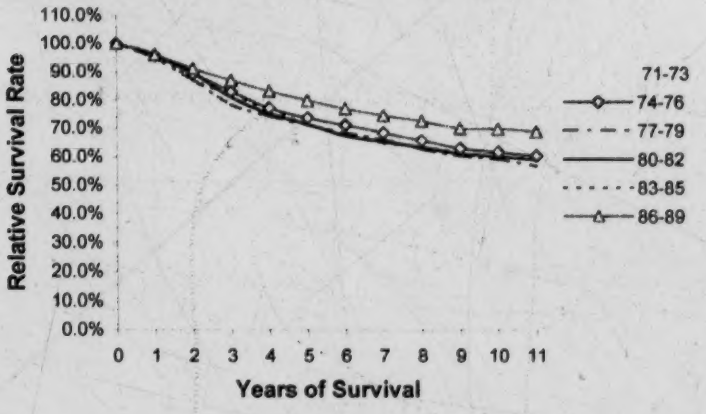


Figure 6.6: Relative Survival by Age Group, Breast Cancer Patients, Northern Alberta, 1971-1989.

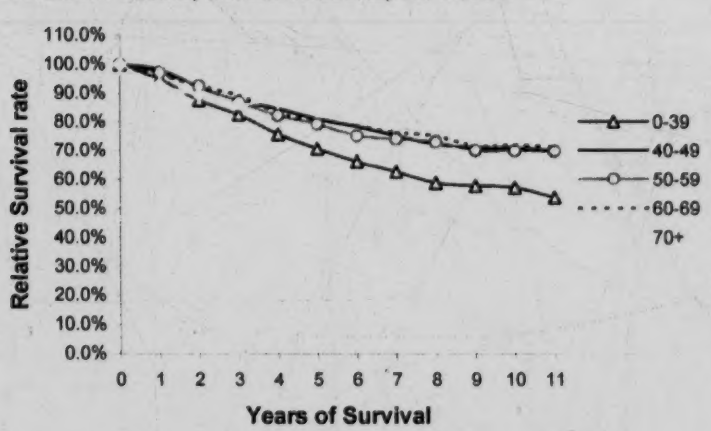


Figure 6.7: Relative Survival by Single Adjuvant Therapy, Breast Cancer Patients, Northern Alberta, 1971-1989.

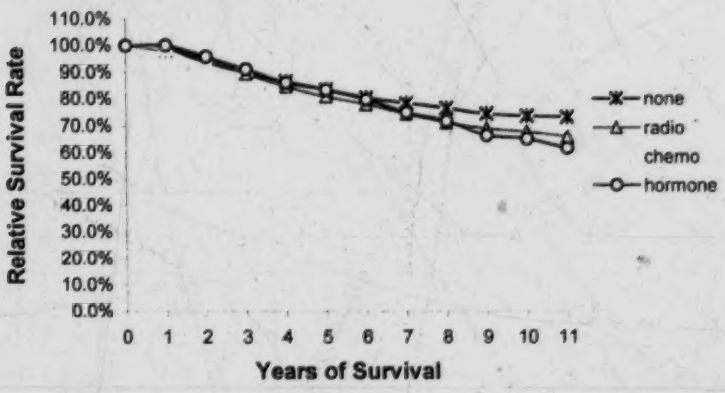
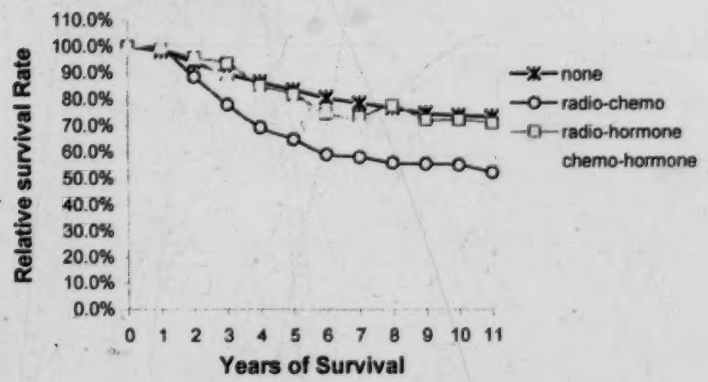


Figure 6.8: Relative Survival by Multiple Adjuvant Therapies, Breast Cancer Patients, Northern Alberta, 1971-1989.



Section 3: PH Cox Regression Model for Predicting Breast Cancer Survival

The following independent variables were initially considered for the multivariate models:

- Age at diagnosis
- Year of Diagnosis Time
- Chemotherapy
- Hormone Therapy
- Radiotherapy
- Surgery
- Clinical Stage
- Tumor Size
- Lymph Node
- Estrogen Receptor
- Progestrogen Receptor
- Morphology Type
- Histology Grade
- Menopausal Status

All selected variables were categorical variables. All variables, except for Menopausal Status, had achieved a statistical significance of p-value ≤ 0.10 in the main effect analyses (described in the previous chapter).

The cause specific survival rates for surgery and no-surgery group were significantly different (Table A-3). Patients with surgical treatment had much better survival compared with patients receiving no surgery (Table A-2). The similar result was

obtained by calculating relative survival too (Table A-25). Patients with lower stages of breast cancer had better survival in both cause specific survival and relative survival (Table A-5). The difference between each pair of stages was statistically significant (Table A-6). The survival rates were significantly different between the subgroups of variable tumor size as well as lymph node (Table A-8, 9, 11, 12). Therefore, surgery, stage, tumor size and lymph node were included in the model building. The results showed that patients with estrogen positive receptor had significantly better cause specific survival rates and relative survival rates (Table A-14, 15). Thus, estrogen receptor was selected as one of the variables for model building. Progestogen receptor is another indication of hormone treatment. However, due to insufficient data, Progestogen receptor was left off the model building. According to the survival calculations, the three morphological subgroups had significant differences in both cause specific and relative survival. The Lobular and Other groups had better survival than Ductular group (Table A-17, 18, 30). Patients with lower histology grade had a significant advantage in survival compared with those with higher histology grade (Table A-20, 21, 31). Based on the above rationale results, morphology type and histology grade were included in the model building. There was a significant difference in survival between pre-menopausal patients and post-menopausal patients (Table A-23, 24, 32). Although at-menopausal patients had no significant difference in survival compared with the patients in pre and post-menopausal status, menopausal status was an interested variable to be taken into account.

Before any actual step of model building was taken, the frequency distribution of subgroups was observed for each variable on the basis of all subjects and subjects with completed data. Except for Age and Diagnosis Time, most of the above variables

contained missing data. We reviewed all the variables to see whether or not it was appropriate to add each individual into the model. We found that only 38 patients had stage IV breast cancer when diagnosed. Patients with stage IV breast cancer usually received palliative (chemo- and radiation) treatment instead of surgery and adjuvant treatment because of metastases. However, adjuvant treatment was the primary treatment of interest in this study. Besides, patients in stage IV occupied only 6.4 percent in all subjects, which was much less than patients in the other three stages (Table A-4). Therefore, we removed 38 subjects with stage IV breast cancer from the model building. After subjects with stage IV breast cancer were removed from the model building, only four subjects had not received surgery. Therefore, these cases were removed and the variable Surgery was eliminated from the model building. The variable Progestogen Receptor was an indicator of hormone therapy as well as Estrogen Receptor. We decided to remove this variable because data were missing in 44.5% of cases. Although variable Estrogen Receptor had missing data too, it was kept in the model since we felt it was an important factor with regard to hormone therapy. Also, we removed the variable histology grade as this information was missing in 66.7 % of cases (Table A-19). We removed variables with too much missing data because the computer would not count and automatically eliminated a subject from the Cox regression procedure if missing datum was existed in any variable for a particular subject. The frequency distribution of subgroups of Menopausal Status uneven. Patients with at-menopausal status occupied a very small percentage of cases (only 4.4%, Table A-22), which may result in skewed outcomes. In addition, the statistical significance of the main effect of Menopausal Status was larger than 0.10. Therefore, it was also eliminated from the model.

The following variables not only had a statistically significant p-value of less than 0.10 in the analysis of main effect, but also had a strong biological or clinical association with the survival of breast cancer. Therefore, they were entered into the model.

- Age
- Diagnosis Time
- Chemotherapy
- Hormone Therapy
- Radiotherapy
- Clinical Stage
- Tumor Size
- Lymph Node
- Estrogen Receptor
- Morphology Type

The information about tumor size and number of positive lymph nodes should have been considered upon classification of clinical stage of breast cancer. Patients with larger tumor sizes, or more positive nodes had advanced clinical stage of breast cancer. On the other hand, clinical stage could reflect a certain degree of information related to tumor size and lymph nodes. In order to include as many subjects as possible as well as to reduce the influence of missing data on the statistical analysis, we decided to build two statistical models of breast cancer survival in this study. One included clinical stage and the other included tumor size and lymph node.

1. Model I

The selected variables for model I included age, diagnosis time, chemotherapy, hormone therapy, radiotherapy, clinical stage, estrogen receptor, and morphology type. All variables achieved at least a statistical significance of p-value less than 0.10 in the analysis of main effect. Forward stepwise PH regression procedure was used to add the variables in the model based on maximum likelihood ratios. Since adjuvant therapies were the primary interest of this study, chemo-, hormone, and radiotherapy were added in the model before the other variables. The rest of the variables were added in one by one based on the value of maximum likelihood ratios. Variables with larger ratios were added in first. This model included 4827 subjects.

The final model of Model I contained following variables: Radiotherapy, Chemotherapy, Hormone therapy, Stage, Morphology Type, Estrogen Receptor, Diagnosis Time, and Age.

2. Model II

The selected variables for model II included age, diagnosis time, chemotherapy, hormone therapy, radiotherapy, tumor size, lymph nodes, estrogen receptor, and morphology type. All variables achieved a statistical significance of p-value less than 0.10 in the analysis of main effect. Forward stepwise regression procedure was used to add the variables in the model. There were 2822 subjects in the analysis.

The final model of Model II included following variables: Chemotherapy, Radiotherapy, Hormone Therapy, Lymph Nodes, Tumor Size, Estrogen Receptor, Morphology Type, Diagnosis Time, and Age.

3. Results

Model I: **Model II:**

Radiotherapy	**Chemotherapy**
Chemotherapy	**Radiotherapy**
Hormone Therapy	**Hormone Therapy**
Clinical Stage	**Lymph Nodes**
Morphology	**Tumor**
Estrogen Receptor	**Estrogen Receptor**
Diagnosis Time	**Morphology**
Age	**Diagnosis Time**
	Age

1) Results of Model I (Table 7.1)

Model I demonstrated that adjuvant chemotherapy, radiotherapy and hormone therapy are independent negative predictors of breast cancer survival. Patients who received adjuvant radiotherapy had a statistically significant hazards ratio (1.2) of dying contrasted with the baseline group of patients who did not receive radiotherapy. The chemotherapy group obtained a significant hazard ratio (1.2) compared with no chemotherapy group. The hormone therapy group had significant hazard ratio (1.2) compared with the no hormone therapy group. The result of radiotherapy, chemotherapy or hormone therapy showed that treatment group had higher hazards ratio of dying than its baseline group. However, we noticed that chemotherapy was usually given to patients with more severe or later stages of breast cancer in clinical practice. Therefore, it would not be difficult to understand that patients who received chemotherapy had higher risk of dying than patients who did not received chemotherapy as their cancer worsened.

Clinical stage was confirmed as independent variable of breast cancer survival as well. Patients with stage II breast cancer had a significant hazard ratio of 2.2 compared with patient with stage I breast cancer. In other words, patients with stage II breast cancers had 2.2 times the risk of dying than patients with stage I breast cancers. Patients with stage III breast cancers had a significant hazard ratio of 4.8 compared with patients

with stage I breast cancers. Although we have tried to adjust for the seriousness of the disease by taking clinical stage possibly into account we may have under-adjusted as clinical stage may be too crude a measure of disease seriousness.

Morphology type was also identified as a predictor variable in the model. Patients with breast cancer whose morphology type was other than Ductular and Lobular had a statistically significant 0.5 hazard of dying, which was less than baseline hazard 1 in the Ductular group. The Lobular group had a statistically significant (p-value 0.078) hazard ratio less than 1 (0.9). Therefore, the predicted survival was better for the Other group and Lobular group comparing with the baseline Ductular group. Another independent variable was Estrogen Receptor. The model predicted that estrogen receptor positive group showed a significant hazard ratio of 0.7 compared with the baseline (estrogen receptor negative group). We can say that patient with positive estrogen receptor had better survival than patients with negative estrogen receptor, and the difference in survival is around 30%. Diagnosis Period and Age were also two identified variables in the model. Patient diagnosed between 1986 and 1989 had a significant hazard ratio of 0.8 compared with the baseline group in which patients were diagnosed before 1980. Patient diagnosed between 1980 and 1985 had no significant difference in hazard ratio comparing with baseline group. The model also predicted that patients at age 40-49 and 50-59 had hazard ratio of 0.8 (The result of the former is slightly lower.), which was highly significant and p-value was 0.004 or 0.023. Therefore, the predicted survival for patients at age 40-49 or 50-59 was significantly better than that of patients at age less than 40, the baseline group. Patients at age 60-69 or 70+ had difference in hazard ratio comparing with baseline group but not significant.

2) Results of Model II (Table 7.2)

Model II used Lymph Node and Tumor Size as two independent variables instead of Clinical Stage as in model I. The predicted hazard ratio was 2.9 for the nodes positive group comparing with nodes negative group. The p-value of significance was 0.000 for the hazard ratio of nodes positive group. The baseline group for Tumor Size was the patients with tumors less than 2 centimeters. Patients with tumors between 2 and 5 centimeters or with tumors more than 5 centimeters had significant (p-value 0.000) hazard ratios of 1.6 and 2.5 respectively, which means they have worse survival than the baseline group. Only chemotherapy had significant impact on survival (p-value 0.012) in model II that was not found for radio- and hormone therapy.

Morphology type was also identified as a predictor variable in model II. Patient with breast cancer whose morphology type was other than Ductular and Lobular had a statistically significant 0.6 hazard of dying, which was less than baseline hazard 1 in the Ductular group. The Lobular group had a hazard ratio equal to 1, but which was not significant. Therefore, the predicted survival was better for Other group comparing with the baseline Ductular group. Another independent variable was Estrogen Receptor. Again, the model predicted that both estrogen receptor positive group showed a significant hazard ratio of 0.7 compared with the baseline (estrogen receptor negative group). We can say that patients with positive estrogen receptor had a better survival than patients with negative estrogen receptor. Patients diagnosed between 1983 and 1985 had a significant difference in hazard ratio of 1.3 compared with baseline group. Patients diagnosed between 1986 and 1989 had a significant difference in hazard ratio of 0.9 compared with baseline group. Model II also predicted that patients in both age groups

40-49 and 50-59 had significant hazard ratio of 0.8 comparing with baseline group. Again, the predicted survival for patients at age 40-49 or 50-59 was significantly better than that of patients at age less than 40.

3) Comparison of Results for Model I and Model II (Table 7.3)

The results of two models of breast cancer survival were partially consistent. The results of the other group in morphology type were consistent between two models. Both models predicted that Other group had better survival than Ductular group. However, for Lobular group, the results were possibly inconsistent. Model I showed that Lobular group had a significant better survival than Ductular group. Model II showed no difference between those two groups in survival. Thus, the result was not significant. The results of estrogen receptor were consistent between two models and predicted better survival in estrogen receptor positive group comparing with estrogen receptor negative group. Also, the results for 1986 to 1989 diagnosis period were consistent between two models. Both model predicted patients had better survival in this group comparing with patients diagnosed before year of 1980. For age group 40-49 and 50-59, both groups predicted better survival compared with baseline (age less than 40) group. In addition the results were possibly consistent in diagnosis period 1983-85 and age group 60 to 69.

However, the results for adjuvant therapy were inconsistent between the two models. In Model I radiotherapy, chemotherapy and hormone therapy were all associated with increased risks of mortality. However, in Model II chemotherapy was associated with a reduced risk of mortality while radiotherapy and hormone therapy were not associated with statistically significant changes in mortality risk.

Table 7.1: Cox Model I

	Hazard Ratio	95% CI
Radiotherapy	1.2	(1.1, 1.3)
Chemotherapy	1.2	(1.0, 1.4)
Hormone Therapy	1.2	(1.0, 1.4)
Stage 2	2.2	(1.9, 2.5)
Stage 3	4.8	(4.2, 5.5)
Morphology G2	0.5	(0.4, 0.6)
Morphology G3	0.9	(0.8, 1.1)
Estrogen Receptor (+)	0.7	(0.6, 0.8)
Estrogen (missing)	0.7	(0.6, 0.8)
Period 2	1.0	(0.9, 1.2)
Period 3	1.1	(0.9, 1.3)
Period 4	0.8	(0.7, 0.9)
Age Group 2	0.8	(0.7, 0.9)
Age Group 3	0.8	(0.7, 0.9)
Age Group 4	1.0	(0.8, 1.2)
Age Group 5	1.0	(0.8, 1.2)

Note 1: 95% CI calculation based on Exp(lnRR ± 1.96*SE).
Note 2: Variable categorizations refer the data definitions in chapter 3.

Table 7.2: Cox Model II

Variable	Hazard Ratio	95% CI
Chemotherapy	0.8	(0.7, 1.0)
Radiotherapy	1.0	(0.9, 1.1)
Hormone Therapy	1.0	(0.8, 1.2)
Nodes Positive	2.9	(2.5, 3.4)
Tumor 2	1.6	(1.4, 1.8)
Tumor 3	2.5	(2.0, 3.1)
Estrogen Receptor (+)	0.7	(0.6, 0.8)
Estrogen (missing)	0.7	(0.6, 0.9)
Morphology 2	0.6	(0.5, 0.8)
Morphology 3	1.0	(0.8, 1.2)
Period 2	1.1	(0.9, 1.4)
Period 3	1.3	(1.1, 1.6)
Period 4	0.9	(0.7, 1.1)
Age Group 2	0.8	(0.6, 1.0)
Age Group 3	0.8	(0.6, 1.0)
Age Group 4	1.0	(0.8, 1.3)
Age Group 5	0.9	(0.7, 1.2)

Note 1: 95% CI calculation based on Exp(lnRR ± 1.96*SE).
Note 2: Variable categorizations refer the data definitions in chapter 3.

Table 7.3: Comparison of Model I and Model II

	Model I Hazard Ratio	Model II Hazard Ratio
Radiotherapy	1.2*	1.0
Chemotherapy	1.2*	0.8*
Hormone Therapy	1.2*	1.0
Stage 2	2.2*	/
Stage 3	4.8*	/
Nodes Positive	/	2.9*
Tumor 2	/	1.6*
Tumor 3	/	2.5*
Morphology G2	0.5*	0.6*
Morphology G3	0.9*	1.0
Estrogen Receptor (+)	0.7*	0.7*
Estrogen (missing)	0.7*	0.7*
Period 2	1.0	1.1
Period 3	1.1	1.3*
Period 4	0.8*	0.9*
Age Group 2	0.8*	0.8*
Age Group 3	0.8*	0.8*
Age Group 4	1.0	1.0
Age Group 5	1.0	0.9

Note 1: "*" indicates statistically significant.
Note 2: "/" indicates that variable is not contained in the model.
Note 3: Variable categorizations refer the data definitions in chapter 3.

CHAPTER 8

DISCUSSION

We know that the treatment of breast cancer had been changing and improving since 1970s and especially since the 1980s. There was an improvement in survival in many breast cancer studies around the world in this time period. We expected that there could be a correlation between the change of treatment and the improvement in survival of breast cancer in Alberta during this period.

In this study, three basic measurements were used to estimate breast cancer patient survival: observed, cause-specific, and relative survival rates. Comparing the 5-year and 10-year overall survival rates (5-year 70%, 10-year 50%) obtained by Statistics Canada (Gaudette, Siberberger, et al., 1996), 5-year overall survival rate of this study (67.5%) was slightly lower than the result from Gaudette's study since this data was collected from 1971 to 1989 and their data was collected between 1980 and 1990. However, the overall survival rate was not an accurate estimate for breast cancer survival. The cause-specific survival rate is a better measure of survival.

Although some of the breast cancer survival studies found an increasing trend in survival for the time before the mid 1980s, there was no statistically significant improvement found in cause-specific survival for patients from 1971-73 period to 1983-85 period in this study. However, we did find a statistically significant improvement for patients diagnosed between 1986 and 1989 compared with those diagnosed in the early periods. A slight improvement or no change in 5-year relative survival for patients diagnosed in 1983-85 compared with patients diagnosed in 1978-80 was seen for various

European countries in the EUROCARE. Also, Brenner's study results (Brenner, Stegmaier, et al., 1998) revealed that there no major change in breast cancer survival before the end of 1980-84 period in Saarland, Germany. The results of this study were consistent with the results of the above studies. The improvement of survival during period 1986-89 in Alberta was not only found in cause-specific survival but also in relative survival. Although the improvement in relative survival cannot be explained by an increased mortality from the causes other than breast cancer, it can be explained by the improved breast cancer survival itself.

Improvement in survival due to earlier detection might be related to the progress in breast cancer screening. We did see a stage shift in the distribution of staging for patients over time. However, when we stratified patients diagnosed in each time period by stage, the estimates of cause specific survival rate for stage II and stage III patients were significantly different among the subgroups by time period. Therefore, these differences in survival are hardly explained by the increased proportion of earlier stages of breast cancer. In this circumstance, multiple prognostic factors that may affect breast cancer survival should be taken into account.

Two regression models were used to assess whether different adjuvant therapies were associated with survival after adjusting for other predictors of survival. Model I indicated that adjuvant chemotherapy, radiotherapy and hormone therapy had statistically significant association with increased risk of mortality. Model II indicated a reduced risk of mortality chemotherapy and no association with risk of mortality for radiotherapy hormone therapy.

For the other predictors in the model the results were mostly consistent. The results of morphology type (G2), estrogen receptor, age (age 40-49 and 50-59 groups), and diagnosis time (1986-89 diagnosis period) are consistent in the two final models of this study. They were identified as significant prognostic factors for breast cancer survival and they were predicted to have better survival than their baseline groups. The results for diagnosis period of 1983-85 and the results for age group 60-69 were possibly consistent between two models. The results were possibly inconsistent between two models for Lobular group (G3) of morphology type, diagnosis period 1980-82 and age group 70 plus.

In addition, tumor size and nodal status were predicted by model II having significant influence on breast cancer survival. Model I identified that clinical stage was a significant risk factor of breast cancer survival. Although we have tried to adjust for the seriousness of the disease by taking into account of clinical stage possibly we may have under adjusted as clinical stage may be too crude a measure of disease seriousness.

The discrepancies of results between two models could be due to fewer subjects in Model II. Model I had 4827 subjects fit in the model while Model II only had 2822 subjects in the model because of missing data. In other words, differences may exist between the two models. Moreover, different measures of disease severity were used in these two models. Clinical stage was used as the measure of severity of breast cancer in model I. Tumor size and nodal status were used to measure breast cancer severity in model II instead of clinical stage in model I. Although tumor size and number of lymph nodes are two essential elements of the determination of clinical stage, the impacts of

these two factors on breast cancer survival still could not be completely the same as the effect of clinical stage.

The results of this study are quite consistent with some other breast cancer studies in which the Cox PH regression model was also used to identify the prognostic factors significant to breast cancer survival. For instance, a review of all cases of early stage breast cancers at Health System in Minneapolis indicated that age, tumor size, estrogen receptor, and menopausal status are associated with survival. Nodal status and Broders' grade are important prognostic factors and SPF (s-phrase fraction) may also play important role in relation to survival (Swenson, 1998). In this study, morphology type is an important prognostic factor significant to survival, which contains part of similar information as tumor grade in Swenson's study. One thing that should be mentioned here is receipt of chemotherapy showing a significant association with survival in their study as well as in this study (only in Model I). In addition, a Scottish Cancer Registry study that used the Cox model predicted that age, clinical stage, pathological tumor size, nodes status and estrogen receptor all influence breast cancer survival (Twelves, 1998). Here, they covered clinical stage as a significant prognostic factor associated with survival. These studies as well as this study used the same statistical model to identify the prognostic factors correlated with breast cancer survival. They have established some prognostic factors in breast cancer survival. However, this study detected more prognostic factors such as treatment factors including radiotherapy, chemotherapy, hormone therapy (in Model I), which were not covered in the other studies.

CHAPTER 9

CONCLUSIONS

The analyses of this study do not indicate that the improved breast cancer survival in Alberta in recent years is related to adjuvant therapy. Even after adjusting for other predictors of survival radiotherapy, chemotherapy and hormone therapy were related to increased risk of mortality in one model. In an alternate model while chemotherapy was related to increased survival radiotherapy and hormone therapy were not found to be related to survival. Other predictors of survival were largely consistent between the two models and with the results of other studies.

CHAPTER 10

RECOMMENDATIONS

Recommendations for Data Collection

During the entire study process, especially the data merging steps and data quality checking procedures, we found some issues related to data collection. Therefore, I make some suggestions for future data collection here, which may be useful for improving the data quality of ACB facilities.

One of the data collection issues met in this study is the inconsistency of medical records contained in different ACB facilities. For instance, a patient could attend different ACB facilities, and have inconsistent information recorded in her medical record at different ACB facilities. In this circumstance, the information entered into the registry computers should be double-checked if there is any inconsistency found, especially if the information is related to the diagnosis or treatment of the patient's breast cancer. If it is difficult to identify the correct information one, then I suggest that the earliest or the most reasonable record in the chart be entered. If it is possible, the patient or her family can be contacted.

The second issue in the collection of data is the different recording format or diagnostic standards used by medical doctors or health care professionals. For instance, consider the date format 19/04/22 recorded as a patient's date of birth in the chart. One registry took 19 as the year of birth, therefore, the patient's date of birth was considered as April 22, 1919. However, another registry took 22 as the year of birth, therefore, it was regarded that the patient was born on April 19, 1922. Another case is the issue of cause of death. For example, in a patient with a metastasis to the lung, the secondary cause of

death was recorded as carcinoma of breast cancer and primary cause of death as . Bronchopneumonia .since the patient had died long time after the primary diagnosis of cancer. It might be more reasonable if the primary cause of death was considered as breast carcinoma. In some cases, doctors did not record the primary cause of death clearly in the charts.

The third issue is that some important information related to the diagnosis or treatment of breast cancer was not completed resulting in missing data in the registries. For example, some charts do not have patient's date of birth but only have patient's age. Some are not completed in diagnosis of clinical stage. Many charts do not contain pathological stage or histological grade. In these circumstances, the data collections and study analyses can be more difficult. Therefore, we highly suggest that doctors complete the patients' medical records as fully as possible.

The last recommendation is that the scripts in the chart should be clear, which makes the job of data clerks much easier and more accurate. Also, we suggest the data clerks should be more careful when they transfer the data from the charts to the computers, which can reduce errors occurring in the data collection.

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Table A-1. Summary Table for Surgery, Breast Cancer Patients, Northern Albert, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
No-surgery	649	10.6	524	125	19.3
Surgery	5451	89.4	2068	3383	62.1
Total	6100	100	2592	3508	57.5

Missing=30

Table A-2. Cause-Specific Survival for Surgery, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
No-surgery	.7557 (.7223, .7892)	.4005 (.3608, .4401)	.2443 (.2085, .2801)	.1214 (.0928, .1500)
Surgery	.9789 (.9751, .9828)	.8736 (.8646, .8825)	.7857 (.7746, .7968)	.6572 (.6441, .6703)

Table A-3. Log-rank Test for Subgroup of Surgery, Breast Cancer Patients, Northern Alberta, 1971-1989.

	P-value	Chi-Square
Log-rank Test	0.0001	1586.6625

Table A-4. Summary Table of Staging, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
Stage I	1684	31.7	349	1335	79.3
Stage II	2312	43.5	955	1357	58.7
Stage III	919	17.3	614	305	33.2
Stage IV	394	7.4	351	43	10.9
Total	5309	100	2269	3040	57.3

Missing=821

Table A-5. Cause-specific Survival for Staging, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Stage I	.9964 (.9936, .9993)	.9547 (.9447, .9647)	.9065 (.8924, .9206)	.8243 (.8056, .8430)
Stage II	.9852 (.9802, .9901)	.8742 (.8648, .8879)	.7772 (.7598, .7945)	.6268 (.6063, 6473)
Stage III	.9329 (.9166, .9492)	.6557 (.6243, .6871)	.5166 (.4832, .5501)	.3371 (.3045, .3697)
Stage IV	.6351 (.5872, .6830)	.2849 (.2388, .3310)	.1335 (.0993, .1707)	.0594 (.0339, .0849)

Table A-6. Log-rank Test for Subgroups of Staging, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Stage I		Stage II		Stage III		Stage IV	
	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S
Stage I		X		X		X		X
Stage II	0.0001	195.7325		X		X		X
Stage III	0.0001	788.3366	0.0001	286.2021		X		X
Stage IV	0.0001	1973.7966	0.0001	1356.6653	0.0001	295.3715		X
Total	P=0.0001		Chi=2383.6752					

Table A-7. Summary Table for Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
<=2cm	2100	53.2	570	1530	72.9
2cm<size=<5cm	1594	40.4	709	885	55.5
>5cm	253	6.4	153	100	39.3
Total	3947	100	1432	2515	63.7

Missing=2183

Table A-8. Cause-Specific Survival for Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
<=2cm	.9856 (.9805, .9907)	.9271 (.9159, .9384)	.8660 (.8512, .8808)	.7665 (.7479, .7852)
2cm<size=<5cm	.9715 (.9633, 9797)	.8285 (.8097, .8473)	.7315 (.7092, .7538)	.5758 (.5502, .6013)
>5cm	.9364 (.9063, .9666)	.6626 (.6034, .7218)	.5163 (.4529, .5796)	.3859 (.3232, .4487)

Table A-9. Log-rank Test for Subgroups of Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

	<=2cm		2cm<size=<5cm		>5cm	
	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S
<=2cm		X		X		X
2cm<size=<5cm	0.0001	158.2459		X		X
>5cm	0.0001	210.0185	0.0001	37.2137		X
Total	P=0.0001		Chi=267.4825			

Table A-10. Summary Table for Lymph Nodes, Breast cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
Nodes (-)	2306	56.2	558	1748	75.8
Nodes (+)	1797	43.8	1049	748	41.6
Total	4103	100	1607	2496	60.8

Missing=2027

Table A-11. Cause-Specific Survival for Lymph Nodes, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Nodes (-)	.9935 (.9902, .9968)	.9440 (.9345, .9535)	.8881 (.8750, .9011)	.7960 (.7791, .8129)
Nodes (+)	.9665 (.9582, .9749)	.7774 (.7581, .7968)	.6498 (.6275, .6721)	.4734 (.4499, .4970)

Table A-12. Log-rank Test for Subgroup of Positive Nodes, Breast Cancer Patients, Northern Alberta, 1971-1989.

	P-value	Chi-Square
Log-rank Test	0.0001	561.5085

Table A-13. Summary Table for Estrogen Receptor, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
Negative	1224	34.1	595	629	51.4
Positive	2361	65.9	867	1494	63.3
Total	3585	100	1462	2123	59.2

Missing=2545

Table A-14. Cause-Specific Survival for Estrogen Receptor, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Negative	.9401 (.9268, .9534)	.7243 (.6991, .7495)	.6053 (.5776, .6329)	.5276 (.4992, .5559)
Positive	.9795 (.9738, .9853)	.8898 (.8770, .9026)	.8008 (.7843, .8172)	.6497 (.6296, .6698)

Table A-15. Log-rank Test for Subgroup of Estrogen Receptor, Breast Cancer Patients, Northern Alberta, 1971-1989.

	P-value	Chi-Square
Log-rank Test	0.0001	58.5811

Table A-16. Summary Table for Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
Ductular	5078	83.9	2240	2838	55.9
Lobular	497	8.2	189	308	62
Other	476	7.9	129	347	72.9
Total	6051	100	2558	3493	57.7

Missing=63

Table A-17. Cause-Specific Survival for Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Ductular	.9528 (.9469, .9586)	.8173 (.8065, .8281)	.7199 (.7072, .7325)	.5886 (.5745, .6027)
Lobular	.9818 (.9700, 99936)	.8831 (.8546, .9116)	.8134 (.7786, .8482)	.6639 (.6208, .7070)
Other	.9725 (.9577, .9872)	.8820 (.8527, .9113)	.8186 (.7835, .8537)	.7521 (.7124, .7919)

Table A-18. Log-rank Test for Subgroups of Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Ductular		Lobular		Other	
	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S
Ductular	X		X		X	
Lobular	0.0028	8.9278	X		X	
Other	0.0001	49.1034	0.0002	13.6319	X	
Total	P=0.0001		Chi=55.7938			

Table A-19. Summary Table for Histologic Grade, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
His_GradeI	163	8.0	33.0	130	79.8
His_GradeII	1045	51.2	372	673	64.4
His_GradeIII	832	40.8	411	421	50.6
Total	2040	100	816	1224	60.0

Missing=4090

Table A-20. Cause-Specific Survival for Histologic Grade, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
His_Grade I	.9938 (.9815, 1.0000)	.9231 (.8813, .9649)	.8963 (.8482, .9445)	.8103 (.7467, .8740)
His_Grade II	.9826 (.9746, 9906)	.8880 (.8686, .9074)	.7990 (.7742, .8238)	.6645 (.6347, .6944)
His_Grade III	.9455 (.9300, .9610)	.7657 (.7366, .7948)	.6576 (.6249, .6904)	.5191 (.4842, .5541)

Table A-21. Log-rank Test for Subgroups of Histologic Grade, Breast Cancer Patients, Northern Alberta, 1971-1989.

	His_Grade I		His_Grade II		His_Grade III	
	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S
His_Grade I	X		X		X	
His_Grade II	0.0005	12.0532	X		X	
His_Grade III	0.0001	37.7079	0.0001	40.2697	X	
Total	P=0.0001		Chi=65.2918			

Table A-22. Summary Table for Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Frequency	Percent	Failed	Censored	%Censored
Pre-menopause	1763	30.1	769	994	56.4
At-menopause	258	4.4	114	144	55.8
Post-menopause	3837	65.5	1620	2217	57.78
Total	5858	100	2503	3355	57.27

Missing=272

Table A-23. Cause-Specific Survival for Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Pre-menopausal	.9733 (.9658, .9808)	.8364 (.8191, .8537)	.7363 (.7156, .7569)	.6174 (.5945, .6402)
At-menopausal	.9883 (.9752,1.0000)	.8401(.7952, .8850)	.7613 (.7090, .8136)	.6425 (.5836, .7014)
Post-menopausal	.9462 (.9390, .9534)	.8189 (.8064, .8313)	.7251 (.7105, .7397)	.5912 (.5746, .6077)

Table A-24. Log-rank Test for Subgroups of Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.

	Pre-menopausal		At-menopausal		Post-menopausal	
	P-V	Chi-S	P-V	Chi-S	P-V	Chi-S
Pre-menopausal	X		X		X	
At-menopausal	0.9790	0.0007	X		X	
Post-menopausal	0.0076	7.1195	0.2043	1.6117	X	
Total	P=0.0188		Chi=7.9446			

Table A-25. Relative Survival for Surgery, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
No-surgery				
Surgery	.9594 (.9380, .9808)	.8480 (.8103, .8857)	.7890 (.7442, .8338)	.6628 (.6068, .7188)

Table A-26. Relative Survival for Staging, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Stage I	1.0020 (.9968,1.0072)	.9671 (.9539, .9803)	.9302 (.9122, .9482)	.8663 (.8406, .8920)
Stage II	.9899 (.9832, .9966)	.8792 (.8630, .8954)	.7915 (.7713, .8117)	.6503 (.6252, 6754)
Stage III	.9366 (.9179, .9553)	.6528 (.6183, .6873)	.5158 (.4789, .5527)	.3403 (.3031, .3775)
Stage IV	.6248 (.5746, .6750)	.2764 (.2293, .3235)	.1279 (.0920, .1638)	.0584 (.0315, .0853)

Table A-27. Relative Survival for Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
<=2cm	.9899 (.9830, .9968)	.9397 (.9258, .9536)	.8941 (.8760, .9122)	.8147 (.7901, .8393)
2cm<size=<5cm	.9737 (.9632, .9842)	.8337 (.8119, .8555)	.7383 (.7122, .7644)	.5919 (.5606, .6232)
>5cm	.9458 (.9127, .9789)	.6670 (.6027, .7313)	.5189 (.4498, .5880)	.4003 (.3282, .4724)

Table A-28. Relative Survival for Lymph Nodes, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Nodes (-)	.9989 (.9940,1.0038)	.9536 (.9416, .9656)	.9072 (.8911, .9233)	.8336 (.8113, .8559)
Nodes (+)	.9737 (.9647, .9827)	.7925 (.7717, .8133)	.6666 (.6423, .6909)	.4955 (.4685, .5225)

Table A-29. Relative Survival for Estrogen Receptor, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Negative	.9433 (.9289, .9577)	.7338 (.7070, .7606)	.6178 (.5880, .6476)	.5527 (.5202, .5852)
Positive	.9848 (.9775, .9921)	.8981 (.8827, .9135)	.8138 (.7941, .8335)	.6809 (.6556, .7062)

Table A-30. Relative Survival for Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Ductular	.9553 (.9485, 1.0021)	.8187 (.8064, .8310)	.7262 (.7117, .7407)	.6065 (.5894, .6236)
Lobular	.9800 (.9630, 9970)	.8986 (.8651, .9321)	.8377 (.7962, .8792)	.7088 (.6550, .7626)
Other	.9752 (.9565, .9939)	.8989 (.8644, .9334)	.8569 (.8151, .8987)	.8057 (.7520, .8594)

Table A-31. Relative Survival for Histologic Grade, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
His_Grade I	.9956 (.9709, 1.0203)	.9166 (.9584, .9748)	.9085 (.8395, .9775)	.8417 (.7440, .9394)
His_Grade II	.9841 (.9731, 9951)	.8970 (.8739, .9201)	.8141 (.7846, .8436)	.7014 (.6639, .7389)
His_Grade III	.9443 (.9265, .9621)	.7720 (.7403, .8037)	.6718 (.6357, .7079)	.5439 (.5032, .5846)

Table A-32. Relative Survival for Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.

	1 year (CI)	3 years (CI)	5 years (CI)	10 years (CI)
Pre-menopausal	.9729 (.9649, .9809)	.8332 (.8151, .8513)	.7330 (.7115, .7545)	.6206 (.5966, .6446)
At-menopausal	.9882 (.9728,1.0036)	.8395 (.7921, .8869)	.7684 (.7134, .8234)	.6703 (.6070, .7336)
Post-menopausal	.9500 (.9413, .9587)	.8253 (.8103, .8403)	.7428 (.7250, .7606)	.6257 (.6036, .6478)

Figures in Appendix:

Figure A-1: Cause-specific Survival Stratified by Surgery, Breast Cancer Patients, Northern Alberta, 1971-1989.

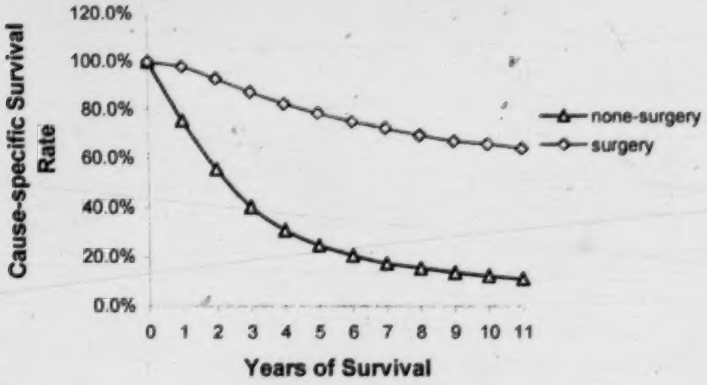

Figure A-2: Relative Survival Stratified by Surgery, Breast Cancer Patients, Northern Alberta, 1971-1989.

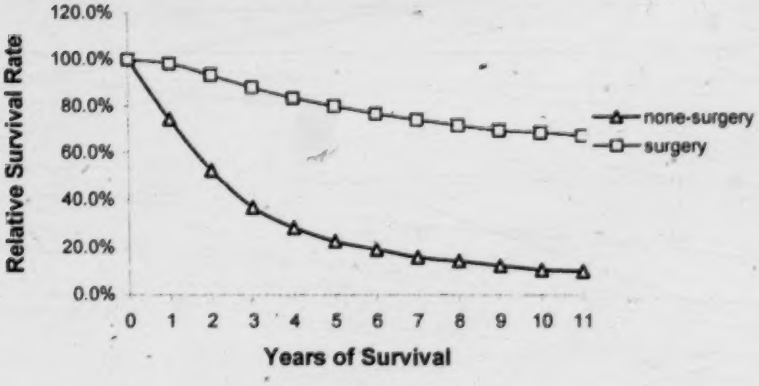

Figure A-3: Cause-specific Survival Stratified by Clinical Stage, Breast Cancer Patients, Northern Alberta, 1971-1989.

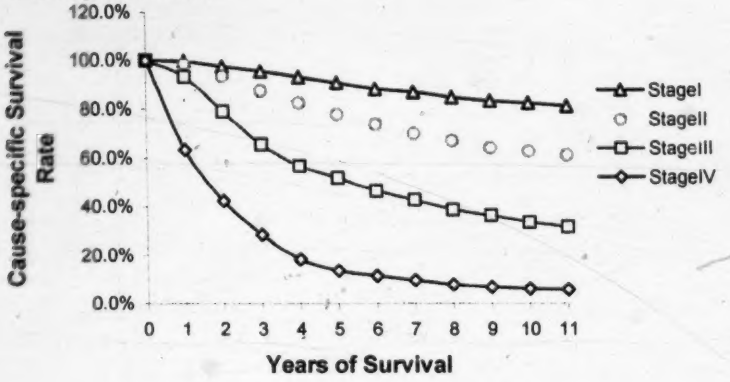

Figure A-4: Relative Survival Stratified by Clinical Stage, Breast Cancer Patients, Northern Alberta, 1971-1989.

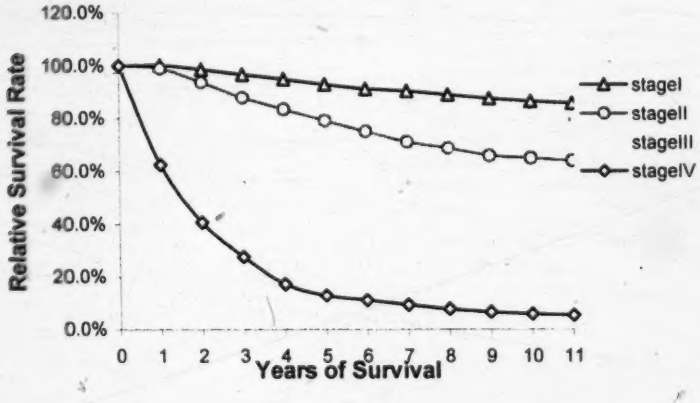

Figure A-5: Cause-specific Survival Stratified by Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

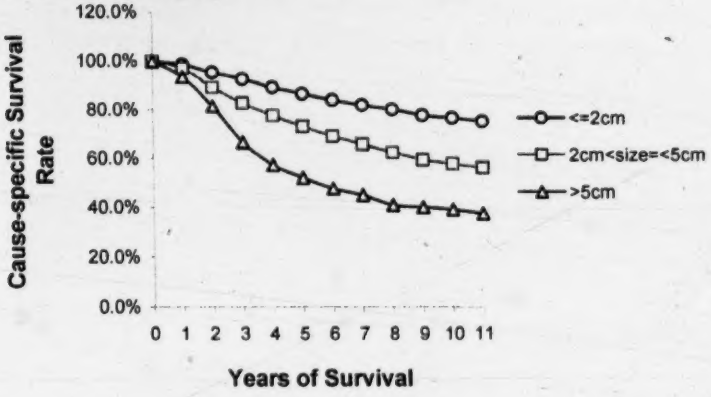

Figure A-6: Relative Survival Stratified by Tumor Size, Breast Cancer Patients, Northern Alberta, 1971-1989.

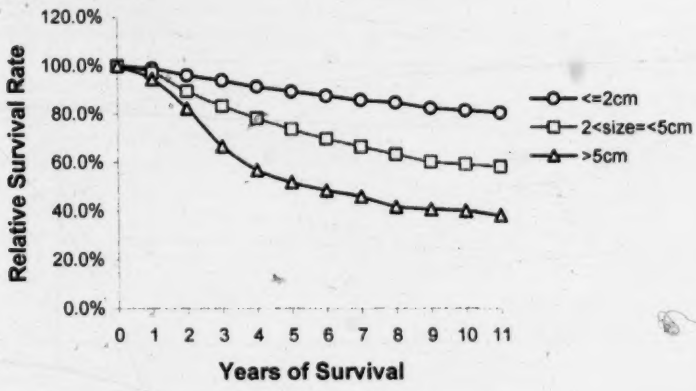

Figure A-7: Cause-Specific Survival Stratified by Lymph Nodes, Breast Cancer Patients, Northern Alberta, 1971-1989.

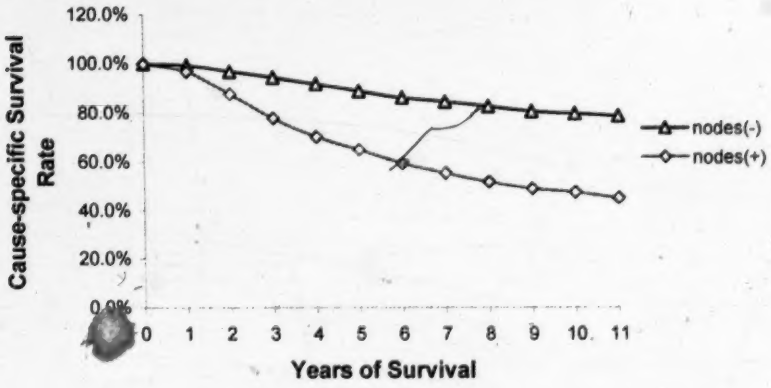

Figure A-8: Relative Survival Stratified by Lymph Nodes, Breast Cancer Patients, Northern Alberta, 1971-1989.

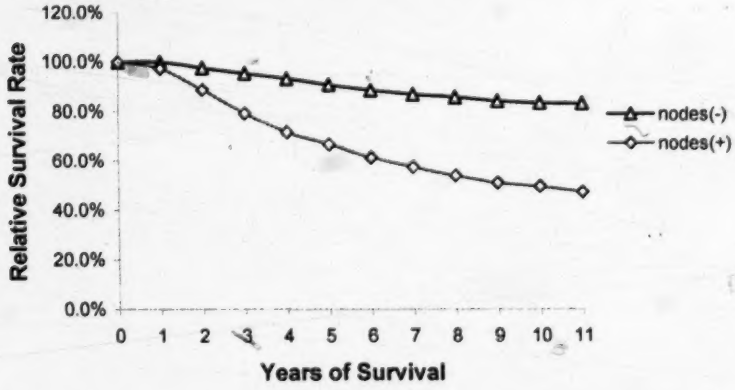

Figure A-9: Cause-specific Survival Stratified by Estrogen Receptor, Breast Cancer Patients, Norhtern Alberta, 1971-1989.

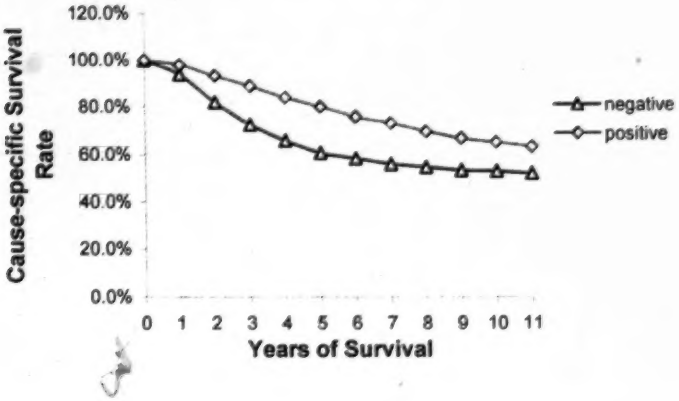

Figure A-10: Relative Survival Stratified by Estrogen Receptor, Breast Cancer Patients, Northern Alberta, 1971-1989.

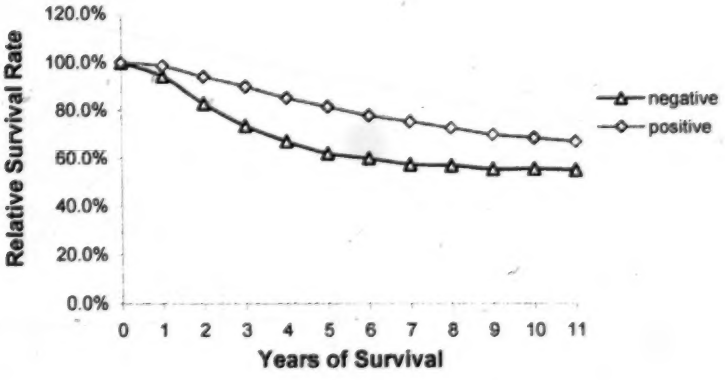

Figure: A-11: Cause-specific Survival Stratified by Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

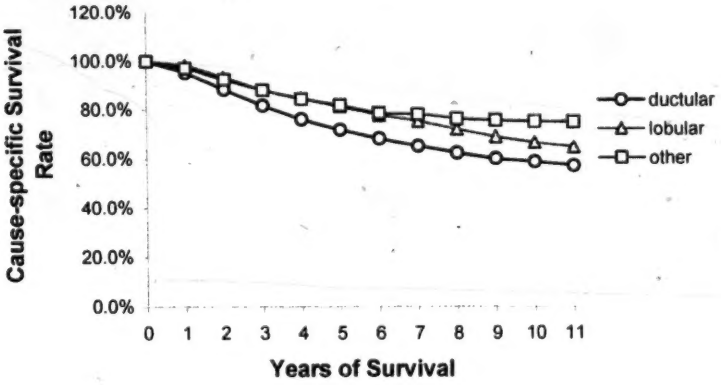

Figure A-12: Relative Survival Stratified by Morphology, Breast Cancer Patients, Northern Alberta, 1971-1989.

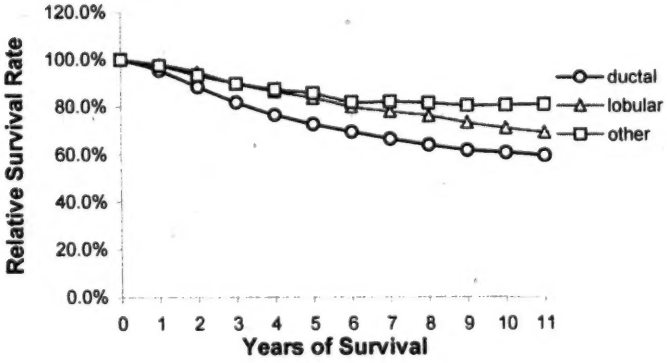

Figure A-13: Cause-specific Survival Stratified by Histologic Grade, Breast Cancer Patients, Norhtern Alberta, 1971-1989.

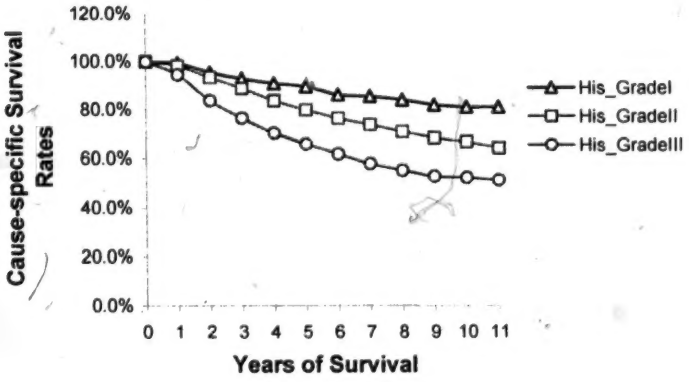

Figure A-14: Relative Survival Stratified by Histologic Grade, Breast Cancer Patients, Norhtern Alberta, 1971-1989.

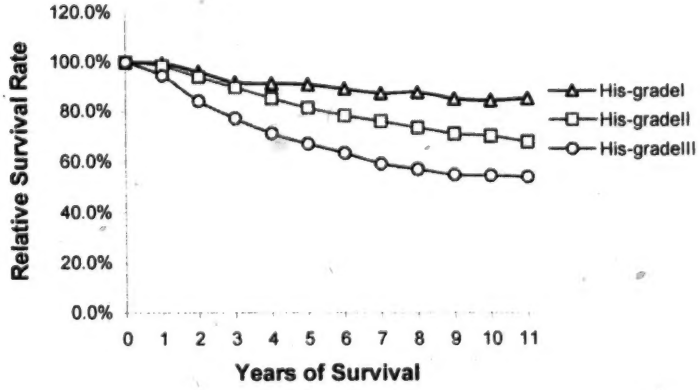

Figure A-15: Cause-specific Survival Stratified By Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.

Figure A-16: Relative Survival Stratified by Menopausal Status, Breast Cancer Patients, Northern Alberta, 1971-1989.